The American Journal of Medicine

July 1955

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Editorial

Subacute Bacterial Endocarditis: Optimal Duration of Treatment. PAUL B. BEESON 1

Clinical Studies

Influence of Gonadal Hormones on Protein-Lipid Relationships in Human Plasma
ELLA M. RUSS, HOWARD A. EDER AND DAVID P. BARR 4

The authors report further on the effects of administration of estrogens and androgens, singly and combined, on the concentration and distribution of plasma lipids and lipoproteins, as measured particularly by the Cohn micro fractionation method; and also on the concomitant clinical results. It is demonstrated unequivocally that estrogens usually reduce abnormally high levels of beta lipoproteins, which are suspected of inducing atherosclerosis, and that androgens elevate them so persistently that concurrent estrogen therapy was ineffectual. The reversion of the plasma lipoproteins toward normal continued only so long as estrogens were administered but protracted therapy was made difficult by the physical and psychologic manifestations of gonadal effects. The clinical usefulness of estrogens in the prevention and treatment of atherosclerosis in man therefore could not be proved. In one case of primary hypercholesterolemic xanthomatosis with hyperlipemia (essential hyperlipemia?) there was dramatic disappearance of tuberous xanthomatous deposits while estrogen therapy could be maintained.

Serum Lipoprotein and Cholesterol Concentrations of Central and North Americans with Different Dietary Habits
GEORGE V. MANN, J. ANTONIO MUÑOZ AND NEVIN S. SCRIMSHAW 25

In this interesting study, the serum cholesterol and lipoprotein concentrations of rural Central American subjects on a vegetarian low fat diet were compared with the corresponding serum constituents of urban Central and North American subjects whose fat intake is liberal. As anticipated, the serum cholesterol levels in the low fat group were significantly lower; however, there was no consistent difference in serum lipoprotein levels. We have here, then, a convenient dissociation between serum cholesterol and lipoprotein concentrations which may make it possible to determine which of these two factors is more important in atherogenesis, at present a subject of hot dispute.

Analysis of 177 Cases of Hypertensive Vascular Disease with Papilledema. One Hundred Twenty-six Patients Treated with Rice Diet
BARBARA NEWBORG AND WALTER KEMPNER 33

In a paper of unusual interest, Dr. Kempner gives what is essentially a five-year follow-up report of his experience with the treatment of hypertensive cardiovascular disease by means of the rice diet.

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THERAPEUTIC BILE

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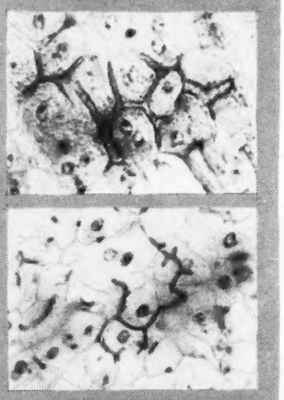

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(1) Clara, M.: Med. Monatsschr. 7:356, 1953. (2) Brauer, R. W., and Pessotti, R. L.: Science *115*:142, 1952. (3) Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. *16*:102, 1953.

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The study is limited to 177 patients with advanced neuroretinopathy, whose average survival rate without treatment would be extremely low. The improvement in symptoms and signs of malignant hypertension, and the increase in survival time of those who could or would adhere strictly to the dietary regimen is unequivocal and impressive, at least in those who did not have significant renal impairment and did not lose significant quantities of sodium in the urine.

Effects of Restriction of Dietary Fat and Cholesterol upon Serum Lipids and Lipoproteins in Patients with Hypertension

FREDERICK T. HATCH, LIESE L. ABELL AND FORREST E. KENDALL 48

In an extension of previous studies on the effect of the unmodified Kempner rice-fruit diet on the serum lipids of hypertensive subjects the authors have investigated the influence upon the serum lipids and lipoproteins of addition of fat, cholesterol and/or protein to the Kempner dietary regimen. The results again indicate that drastic dietary restriction of cholesterol, and also of fat, has comparatively little prolonged influence upon the serum lipid and lipoprotein levels if ample supplies of carbohydrate and protein are made available for biosynthesis of lipids. Most subjects showed some decline in serum cholesterol esters but not consistently in free cholesterol or phospholipid; some showed an increase of neutral fat in the serum. Of interest is the observation that S_f 12–20 lipoproteins did not decrease significantly; S_f 20–100 lipoproteins increased. The study, which was conducted under carefully controlled conditions, supports the general thesis that total caloric intake is of greater significance in relation to maintenance of serum lipid and lipoprotein levels than the quantity of cholesterol or of fat ingested.

Effects of Sitosterol on Serum Lipids

MAURICE M. BEST, CHARLES H. DUNCAN, EDWARD J. VAN LOON AND JOAN D. WATHEN 61

The quest for a practical means of effecting sustained lowering of the serum cholesterol continues in the hope of finding some way of deferring clinically significant atherosclerosis in our aging population. The present study describes the results of incorporation of a plant sterol, beta-sitosterol, into the otherwise free diet in adequately controlled experiments in fourteen human subjects. This sterol, now known to be absorbed from the gastrointestinal tract, apparently interferes with absorption of cholesterol, perhaps by competing for esterification. In any event, the serum cholesterol, total lipid and neutral fat levels fall about 20 per cent, the serum lipid phosphorus and allegedly atherogenic lipoproteins somewhat less. This is an impressive result, although biosynthesis of cholesterol appears not to be depressed and clinical benefit remains to be established. This approach to the problem of prevention of atherosclerosis should be pursued further, it is to be hoped, with the observance of controls and restrained judgments of the present investigators.

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Serum Lipid Pattern in Hyperthyroidism, Hypothyroidism and Coronary Atherosclerosis . . . . . RICHARD J. JONES, LOUIS COHEN AND HOWARD CORBUS 71

The authors combined conventional chemical analysis of serum lipids with ultracentrifugal fractionation of serum lipoproteins, at a density of 1.21, in an attempt to find deviations characteristic of myxedema, particularly in relation to hyperthyroidism and to coronary artery disease. The differences in the first two categories, reflecting the effect of thyroid hormone, were significant notably in respect to increased beta lipoproteins and the more rapidly floating lipoproteins in hypothyroidism. The results in relation to idiopathic hypercholesterolemia with associated coronary artery disease showed much overlapping, a point of interest in connection with the controversial question of the prevalence of coronary atherosclerosis in myxedematous subjects.

Night-eating Syndrome. A Pattern of Food Intake among Certain Obese Patients ALBERT J. STUNKARD, WILLIAM J. GRACE AND HAROLD G. WOLFF 78

This interesting report describes an abnormal eating pattern, characterized by nocturnal hyperphagia, insomnia and morning anorexia, occurring in certain obese patients particularly during periods of weight gain and life stress. Reducing regimens were found to be ineffective in such subjects and, indeed, likely to evoke anxiety or depressive reactions. The authors speculate on significance and etiology of the syndrome.

Review

Metal Chelate Compounds of Urine. Their Relation to the Initiation and Growth of Calculi . WILLIAM H. BOYCE, FRED K. GARVEY AND CHARLES M. NORFLEET, JR. 87

Most of the many theories proposed to explain urinary calculus formation are nebulous, archaic or based upon mass law considerations which are inapplicable. The present able study presents a fresh point of view which is backed up by solid evidence and by suppositions which reasonably account for most of the known facts about stone formation. The authors indicate that abnormal mucoproteins found in the urine of stone-formers act as metal (calcium) chelating agents to form large calcium-mucoprotein complexes, with subsequent crystallization of the stone salts. A similar process might well apply to the formation of bone salts also.

Seminars on Carbohydrate Metabolism

Metabolism of Carbohydrates. A Review . DEWITT STETTEN, JR. AND YALE J. TOPPER 96

Elucidation of the causes of the disorders of carbohydrate metabolism and of the mechanisms of action of insulin, which will be the subjects of the series of seminars to follow, will require understand-

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ing of the normal processes of the intermediate metabolism of carbohydrates and of their interdigitation with fat and protein metabolism. Drs. Stetten and Topper here provide an outstanding summation of present knowledge in this field. Beginning with the processes of photosynthesis, and thus the ultimate origins of biochemical energy, they go on to discuss the pathways of glycolysis, the phosphogluconate oxidation route of glucose degradation, enzymatic interconversions of hexoses, the mechanisms of glycogen storage and breakdown, and end with a brief discussion of other polysaccharides of biologic significance. The reader will find this paper an enlightening introduction to disorders of carbohydrate metabolism.

Combined Staff Clinic

Obesity 111

Combined Staff Clinics (Columbia University College of Physicians and Surgeons)—This conference deals in some detail with current views on the causes and management of the complex problem of obesity in both its metabolic and psychologic aspects. The topics covered include a review of the metabolism of fat and of adipose tissue, a consideration of prevailing theories of appetite control, a discussion of the possible multiple etiologies of experimental and clinical obesity and other relevant aspects. In management, the effectiveness of various special diets and drugs is considered rather cursorily, with the conclusion that restriction of caloric intake, with proper regard to psychologic complications, remains the basic principle of prevention and treatment.

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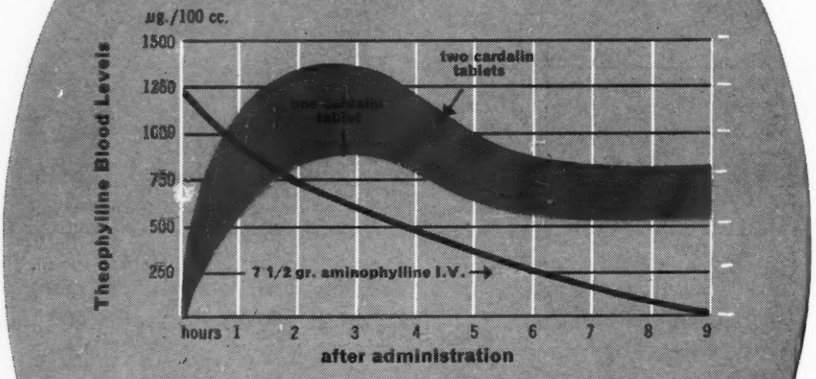
only therapeutic

aminophylline blood levels produce

therapeutic results



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References on the therapeutic efficacy of Cardalin

1. Segal, M. S., et al.: Quart. Rev. Allergy & Applied Immunol. 6: 399, 1952.
2. Levine, E. R.: Med. Rec. & Ann. 46: 322, 1952.
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4. Barach, A. L., et al.: Dis. Chest 23: 121, 1953.
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6. Bickerman, H. A., et al.: Ann. Allergy 11: 309, 1953.

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Retroperitoneal Pneumography in the Diagnosis of Retroperitoneal Lymphomatous Neoplasms . . . . RALPH M. MYERSON AND GEORGE T. WOHL 155

The usefulness of retroperitoneal pneumography by the presacral air injection technic is indicated by illustrative cases of abdominal Hodgkin's disease. A modification of the usual procedure is proposed.

Rupture of Aortic Aneurysm into the Pulmonary Artery. Report of a Case Proved by Cardiac Catheterization . . . . DAVID BUTTROSS, JR. AND JOHN SALATICH 159

Rupture of an aortic aneurysm into the pulmonary artery gives sufficiently distinctive findings to permit a presumptive diagnosis in patients who survive, and confirmatory evidence can be obtained by cardiac catheterization. The authors describe such an event in a patient alive and in fair health nineteen months later.

Errata. In the May 1955 issue of *The American Journal of Medicine:*

1. The Foreword by Dr. Maxwell Finland, p. 683, the second paragraph in the right column should begin: Some of these cases offer a real challenge. First, early diagnosis and treatment of the original infections may help prevent the later chronic and resistant forms.

2. The article entitled "Present Status of the Chemotherapy of Tuberculosis" by Dr. Robert H. Ebert, p. 746, the second paragraph in the right column should read as follows: Streptomycin should not be used in the presence of renal impairment since levels become so elevated if kidney damage is present that eighth nerve damage is likely.[22] The central nervous system effects of isoniazid are more likely to occur in patients with previous histories of convulsions or psychoses, and in such individuals the drug should be discontinued on the first indication of a toxic effect on the central nervous system.[95]

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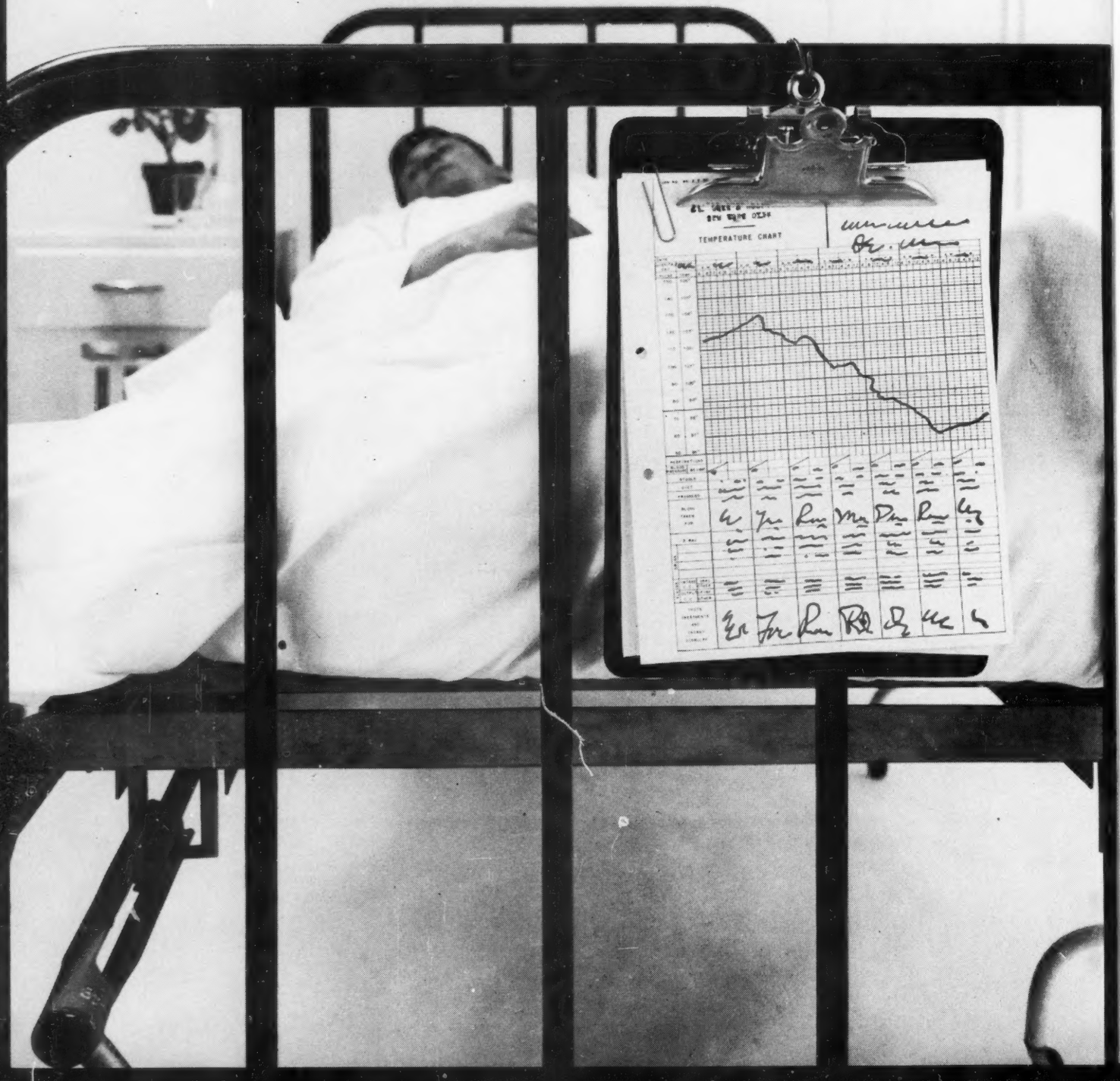

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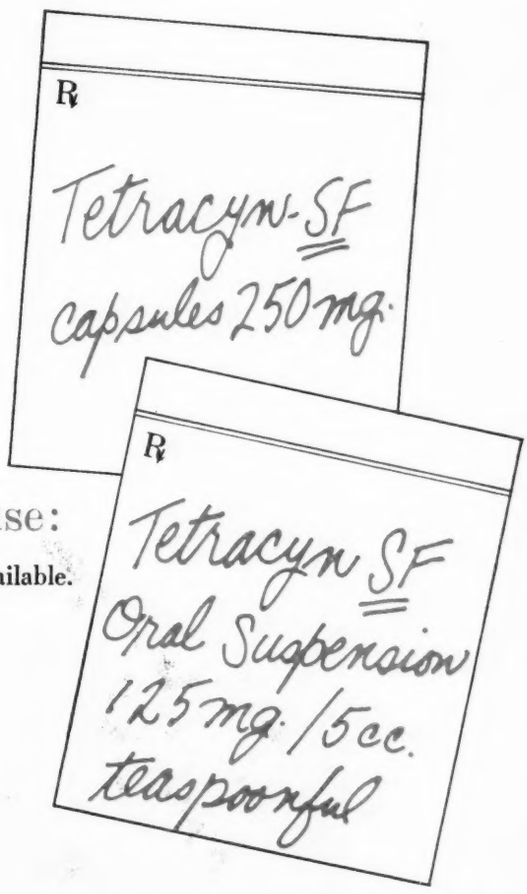

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1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952.
2. Martí-Ibáñez, F: Antibiotic Med. *1*:247 (May) 1955.
3. Dumas, K. J.; Carlozzi, M., and Wright, W. A.: Antibiotic Med. *1*:296 (May) 1955.

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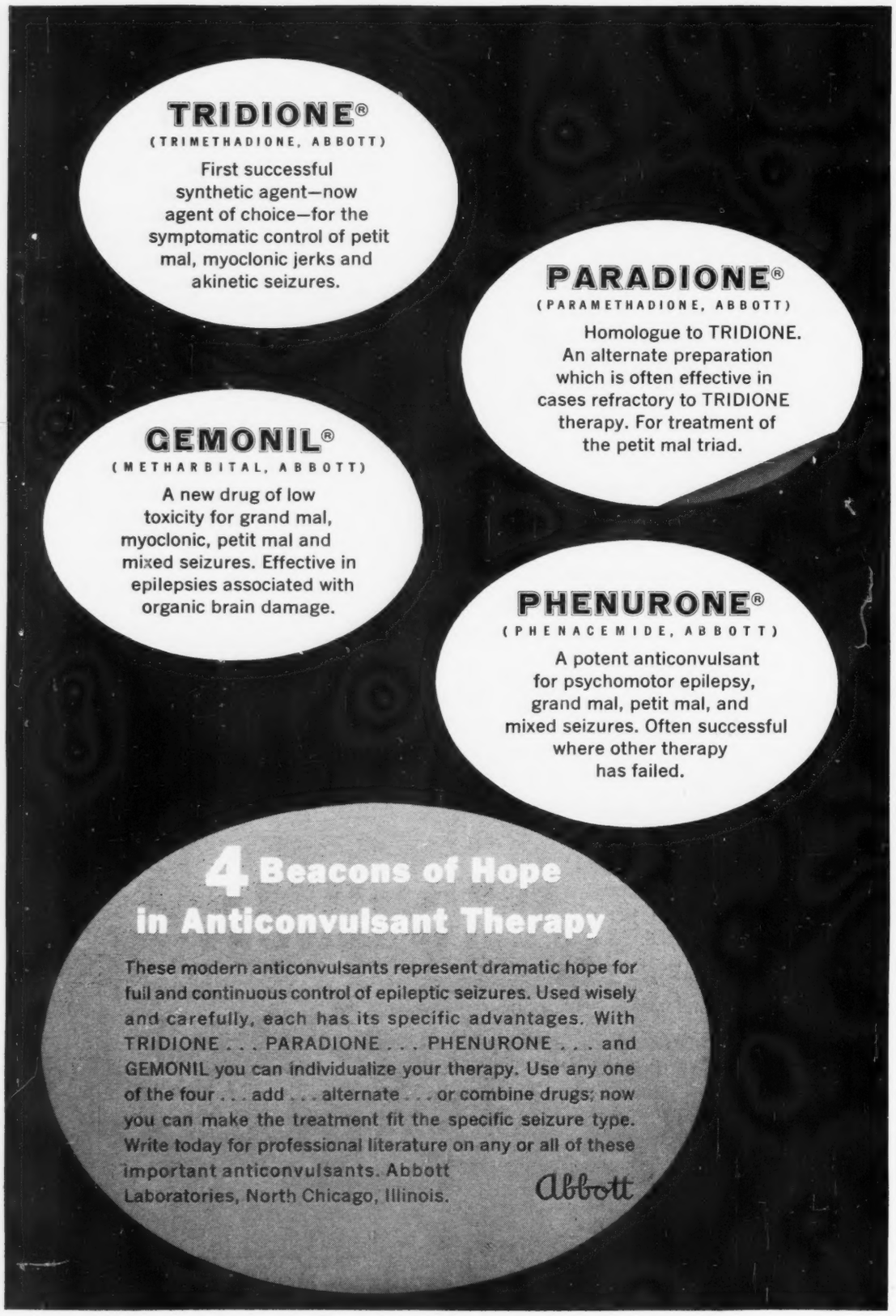
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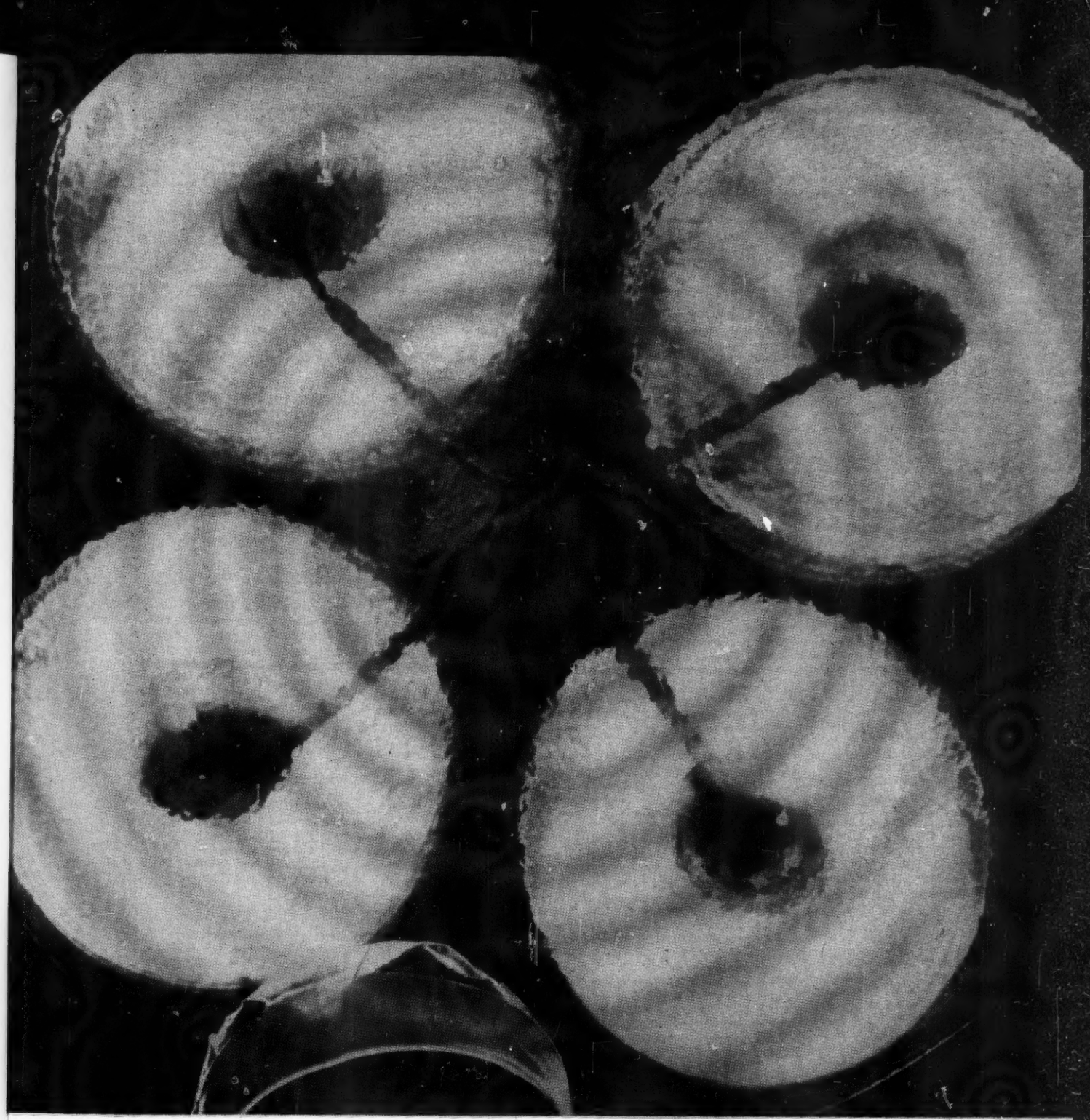

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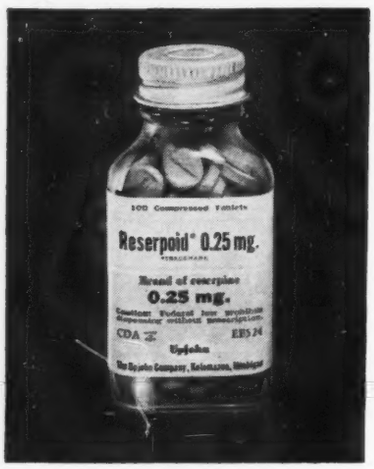

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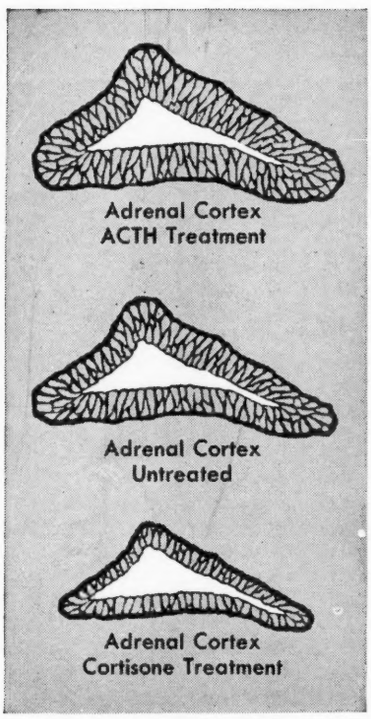

THERE IS A DIFFERENCE BETWEEN ACTH AND CORTISONE

For this reason, the response of the adrenal cortex must be preserved. *It can be preserved* by utilizing the antagonism between ACTH and cortisone or hydrocortisone at the adrenal cortical level.

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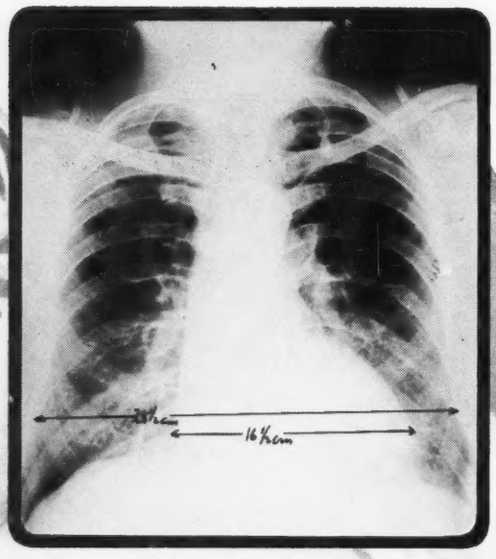
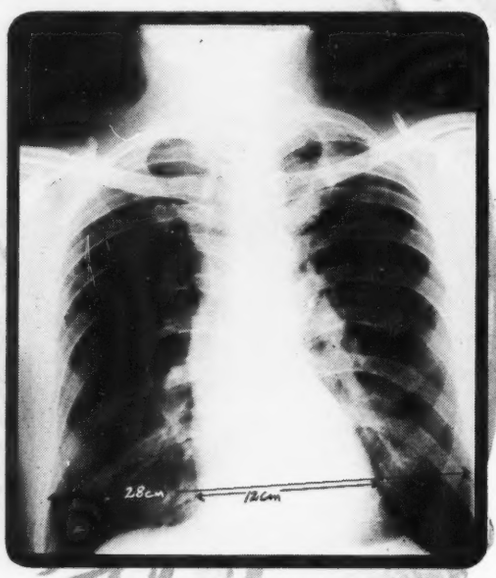


(X-ray, enlarged heart)

ESSENTIAL
HYPERTENSION

AFTER



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1. Overall, J. C.: Southern M. J. 47:789, 1954. 2. Editorial: New England J. M. 246:111, 1952.
3. Grayzel, H. G., Heimer, C. B., and Grayzel R. W.: New York St. J. M. 53:2233, 1953.
4. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
5. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
6. Turell, R.: New York St. J. M. 50:2282, 1950.

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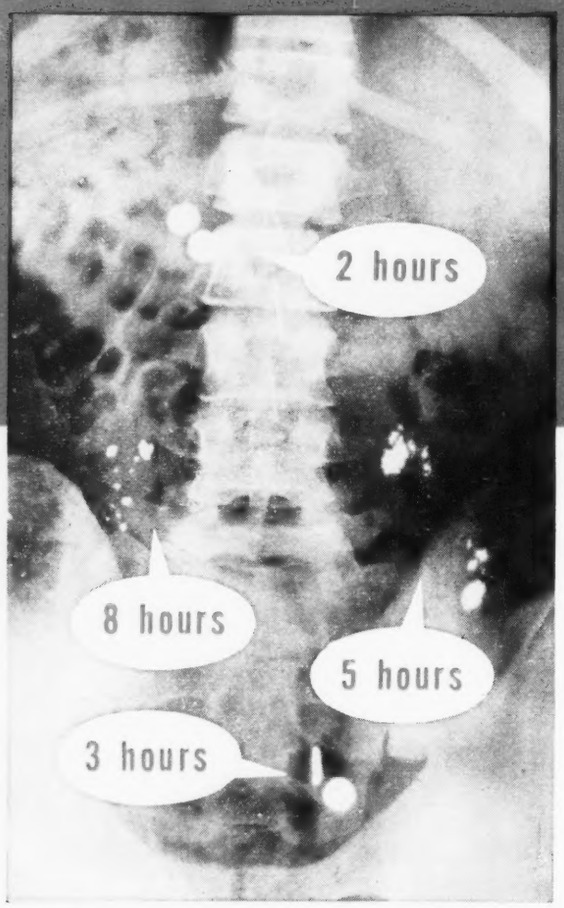

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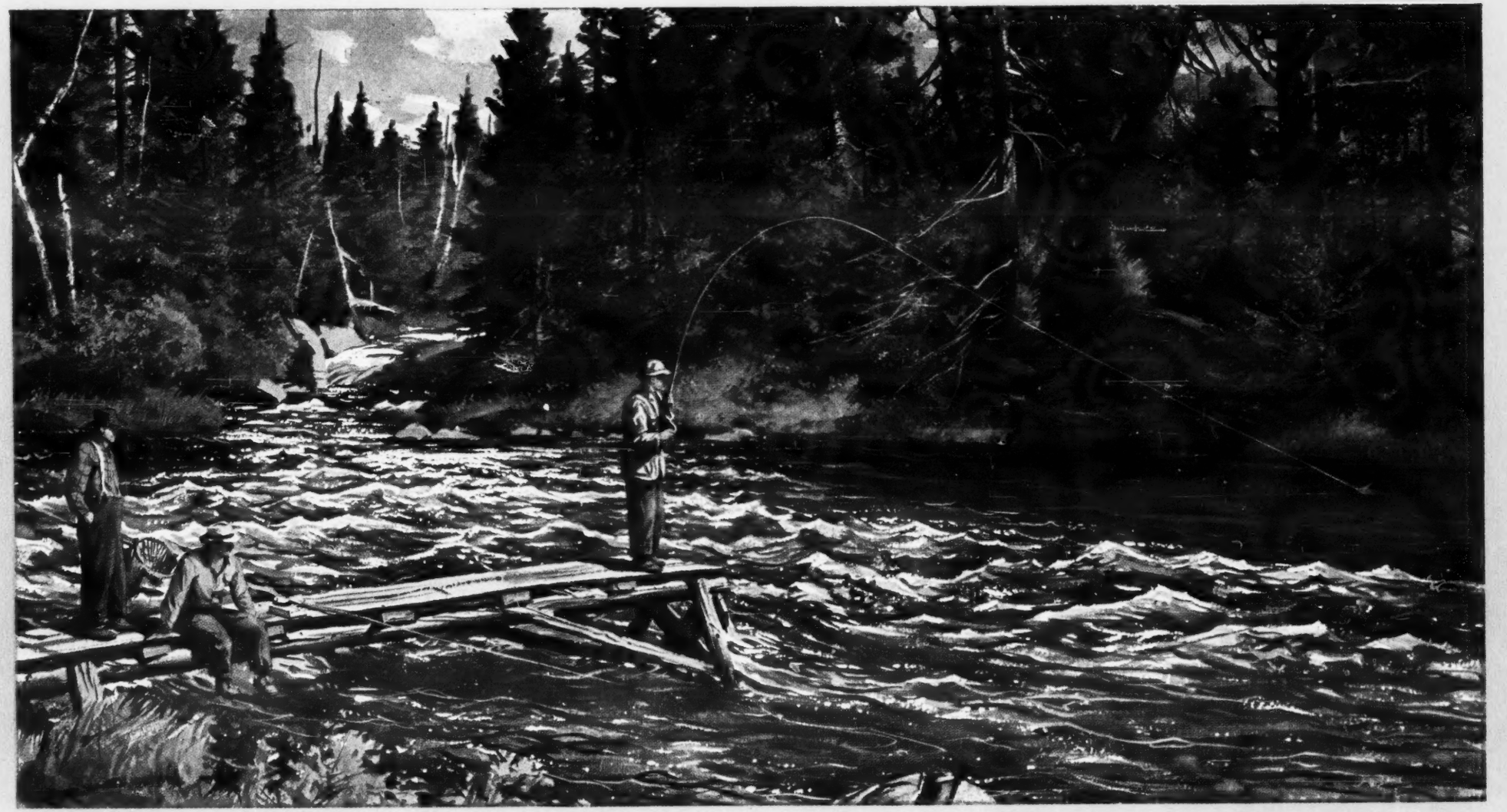

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Finnerty, F.A., Jr.: Am. J. Med. *17*:629 (Nov.) 1954.

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". . . [Rauwiloid] produces certain desirable effects such as mild sedation without somnolence and a general sense of well-being . . ."

Livesay, W.R., et al.: J.A.M.A. *155*:1027 (July 17) 1954.

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". . . more than 70% of the patients said, unasked, that they felt better . . . 'I sleep better,' 'I am less jittery' and 'I feel good' were often heard."

Lipsett, M.B., et al.: California Med. *81*:412 (Dec.) 1954.

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"Its [Rauwiloid's] relaxing action may be responsible in part for the marked symptomatic relief it affords, especially in anxious, neurotic, hypertensive patients."

Wilkins, R.W.: Mississippi Doctor *30*:359 (Apr.) 1953.

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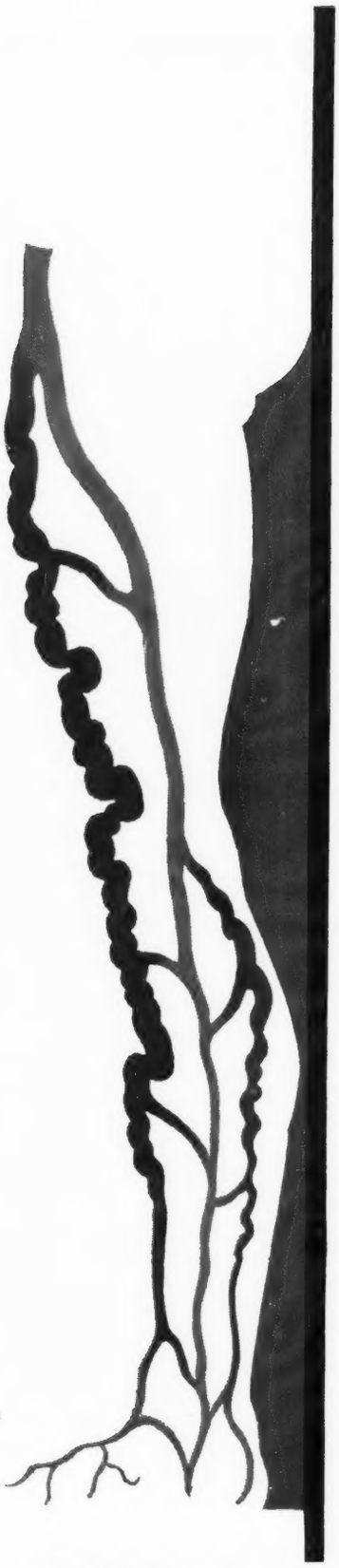

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References: (1) Lawrence, E. D.; Doktor, D., and Sall, J.: Angiology *2*:405, 1951. (2) Rottino, A.; Boller, R., and Pratt, G. H.: Angiology *1*:194, 1950. (3) Boller, R.; Rottino, A., and Pratt, G. H.: Angiology *3*:260, 1952. (4) Pratt, G. H.: Surg. Clin. North America *33*:1229, 1953.

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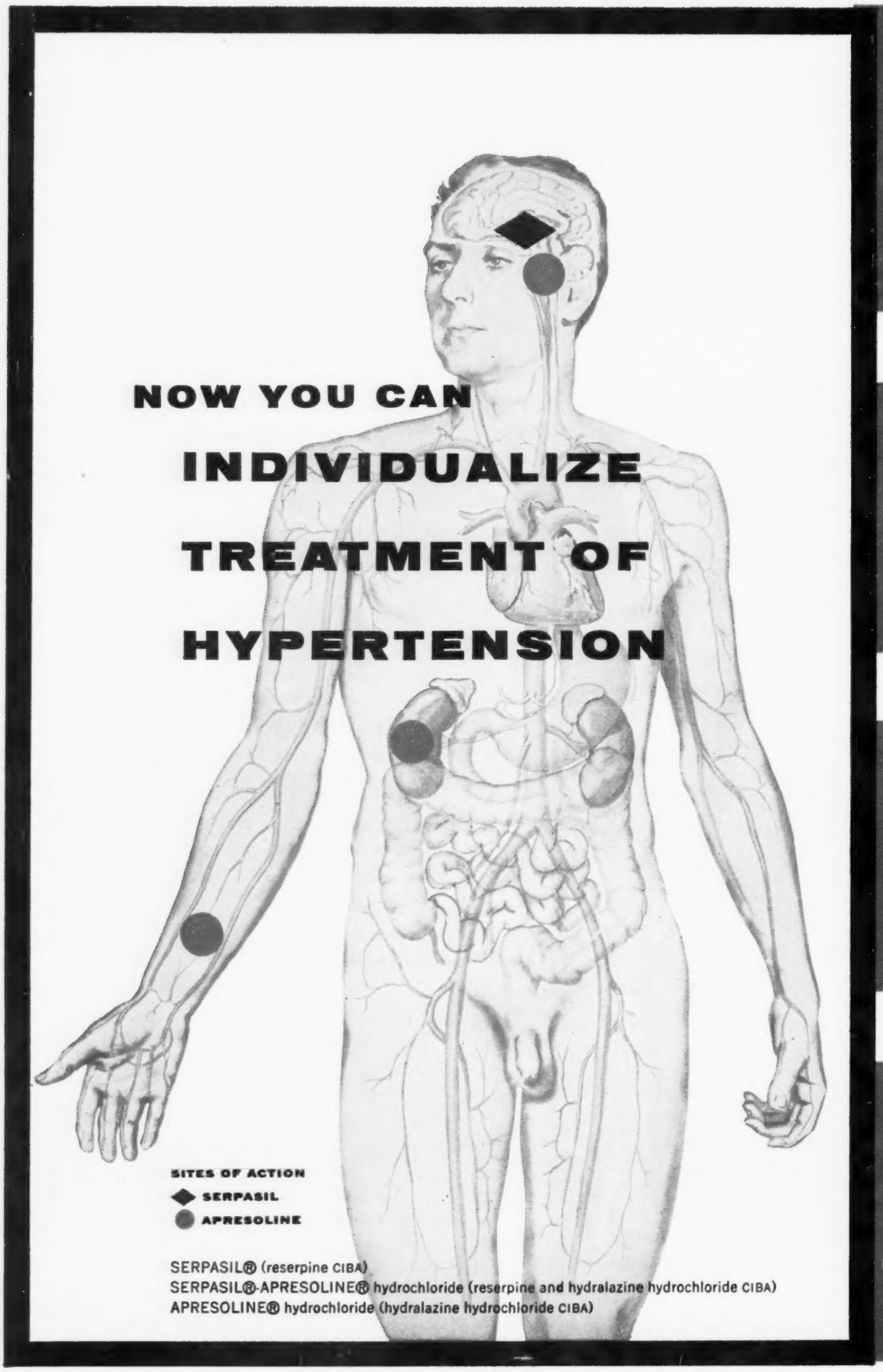
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1. Eisfelder, H. W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954.

2. Sebrell, W. H., Jr.: J.A.M.A., 152:42 (May) 1953.

3. Sherman, R. J., M.D.: Medical Times, 82:107 (Feb.) 1954.

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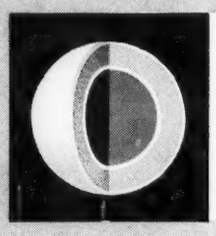
*Ingels, A. H.: California Medicine 79:437, 1953.



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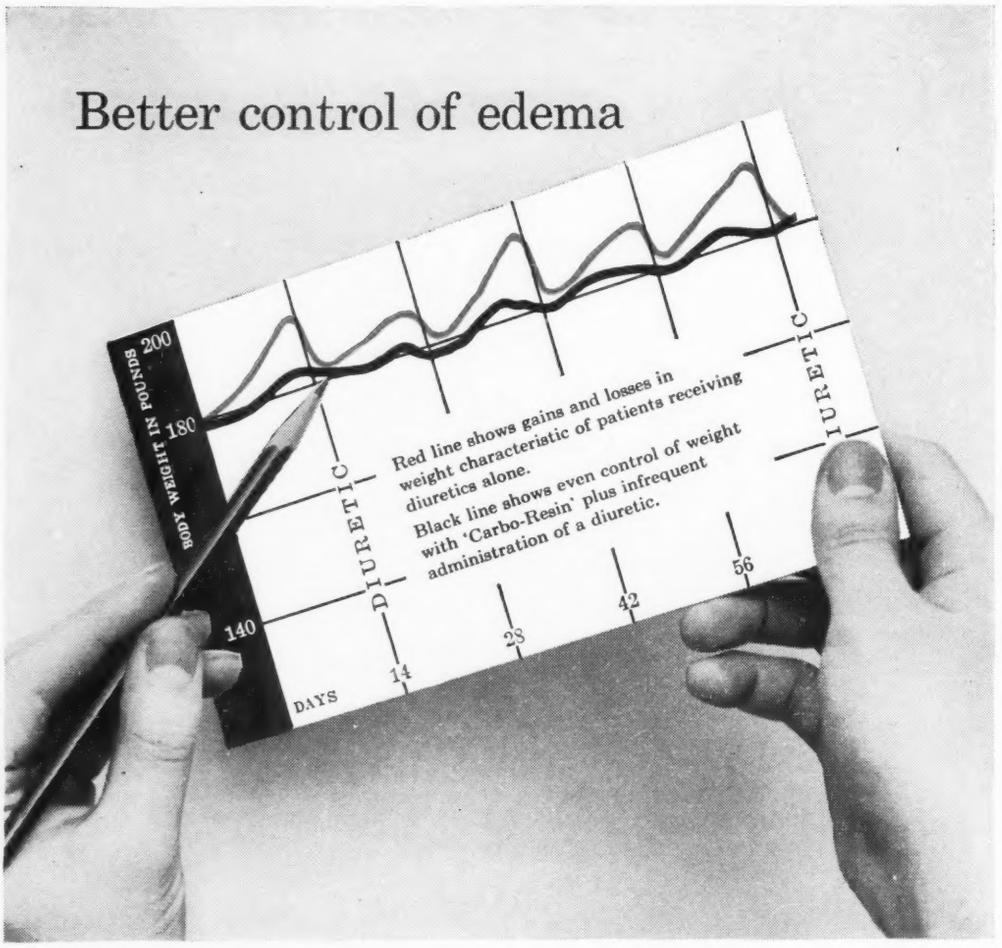

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The American Journal of Medicine

VOL. XIX JULY, 1955 NO. 1

Editorial

Subacute Bacterial Endocarditis: Optimal Duration of Treatment

AFTER a dozen years' experience with antibiotic therapy of subacute bacterial endocarditis certain points have been established: (1) Penicillin is usually much more effective than other antibiotics. (2) Moderately large doses should be given. (3) The period of chemotherapy must be of some length. The aim of this editorial is to consider the evidence bearing on the last point, the optimal duration of antibiotic treatment.

It may be recalled that when penicillin first became available, distribution to physicians in the United States was the responsibility of the National Research Council's Committee on Chemotherapy. In view of great demand and limited supply, this Committee released penicillin with the recommendation that specific doses be employed. Initially the quantity allocated for treatment of a case of bacterial endocarditis was 4,200,000 units, to be given either at the rate of 300,000 units daily for fourteen days or 200,000 units daily for twenty-one days. These schedules of treatment achieved successful results in at least half of the patients treated.[1] Soon it became apparent, however, that some infections required more intensive therapy; consequently, as supplies became more plentiful there was a tendency to give larger doses for longer periods of time.

In 1948 Keefer presented to the Association of American Physicians an analysis of the results of 450 cases collected by the Committee on Chemotherapy, together with 26 cases personally observed.[2] The following two sentences are taken from that report: "It has been demonstrated that the largest number of patients (75 to 80 per cent) recover following an initial course of 500,000 units of penicillin daily for eight weeks. When less than 500,000 units are given daily, and treatment is continued for less than eight weeks, then the relapse rate is high and the number that recover is decreased (60 to 70 per cent)." This statement undoubtedly has had considerable influence on our practice in the treatment of bacterial endocarditis during the succeeding years. Many physicians believe that the safest course is to continue chemotherapy in all cases for six to eight weeks. Finland, in a recent comprehensive review,[3] accepts the view that "large doses must be given continuously over long periods," and states further that, "although large doses given for short periods have sometimes proved effective and have been suggested as a useful form of administration, this method has also been tried and found wanting in many cases." The evidence cited consists of the reports of Hamburger and Stein[4] and of King et al.,[5] both of which will be discussed here in some detail.

There is no doubt that some cases of subacute bacterial endocarditis can be cured by comparatively short courses of penicillin therapy. On various occasions treatment had been discontinued after only ten to fourteen days for one reason or another, yet the infection was found to

[1] MEADS, M., HARRIS, W. and FINLAND, M. The treatment of subacute bacterial endocarditis with penicillin. *New England J. Med.*, 232: 463, 1945.

[2] KEEFER, C. S., ANDERSON, D. G. and HEWITT, W. L. End results in the treatment of bacterial endocarditis. *Tr. A. Am. Physicians*, 61: 112, 1948.

[3] FINLAND, M. Treatment of bacterial endocarditis. *New England J. Med.*, 250: 372, 1954.

[4] HAMBURGER, M. and STEIN, L. Streptococcus viridans subacute bacterial endocarditis. Two week treatment schedule with penicillin. *J. A. M. A.*, 149: 542, 1949.

[5] KING, F. H., SCHNEIERSON, S. S., SUSSMAN, M. L., JANOWITZ, H. D. and STOLLERMAN, G. H. Prolonged moderate dose therapy versus intensive short term therapy with penicillin and caronamide in subacute bacterial endocarditis. *J. Mt. Sinai Hosp.*, 16: 35, 1949.

have been eradicated. In 1949 Hamburger and Stein reported their experience with twelve patients each of whom had been treated for two weeks, 15,000,000 or 16,000,000 units of penicillin being given daily either by continuous intravenous injection or by intermittent intramuscular injection. There were two deaths in the series, neither one due to continuing infection; two patients had relapses within one month but were successfully retreated according to the same schedule; the remaining eight had been cured by the first course of treatment. Hunter in 1952 mentioned five patients, all of whom had responded satisfactorily to treatment consisting of 2,500,000 units of penicillin and 2 gm. of streptomycin daily for only ten days.[6]

Hunter had shown by laboratory experiment that streptomycin enhances the bactericidal effect of penicillin on enterococcus and on some of the other nonhemolytic streptococci. Robbins and Tompsett confirmed the effectiveness of this combination in the therapy of enterococcus infection.[7] Although its value is less certainly established in endocarditis caused by other kinds of streptococci, many clinicians have adopted the practice of employing it in all cases involving nonhemolytic streptococci.

Let us now examine the main pieces of evidence that have provided the basis for belief that long courses of therapy are safest for the treatment of all cases.

1. The conclusion of Keefer and his associates, based on analysis of the early cases treated under supervision of the Committee on Chemotherapy, has already been mentioned. It should be noted that the data were obtained during early experiences with penicillin when doses were small, as measured by present standards, and that the combination of streptomycin with penicillin was not then being used.

2. Cates and Christie in 1951 reviewed their experiences with more than 400 patients treated in Great Britain under the auspices of the Medical Research Council.[8] In early trials an experiment to assess the importance of duration of treatment was conducted on three groups of patients, all of whom received a total dose of 5,000,000 units. Those in one group were given 1,000,000 units daily for only five days; treatment failed in 83 per cent. Patients in the second group received 500,000 units daily for ten days; 50 per cent were failures. Those in the third group received 250,000 units daily for twenty days and only 22 per cent were failures. This demonstrates clearly the importance of duration of therapy in determining outcome; however, treatment periods employed in the early trials may not be applicable to present-day practice because of the small amounts of penicillin given and because streptomycin was not being used as an adjuvant.

3. The clinical experiment of King et al.,[5] carried out in 1948, is of great interest and its result also has had considerable influence. The purpose of the experiment was to determine the effectiveness of massive antibiotic therapy given for a period of ten days. Eight patients infected with organisms sensitive to penicillin were included in the study. Each one received ten rapid intravenous injections of 1,000,000 units of penicillin at hourly intervals each day; during the remainder of the twenty-four hour period four additional intramuscular injections of 1,000,000 units were given. Thus the total quantity of penicillin administered to each patient was 14,000,000 units per day. In order to increase the already high tissue levels of penicillin, caronamide was given. The results obtained were extraordinarily poor; only one of the eight patients was cured, yet four of the remaining seven later responded satisfactorily to treatment consisting of 400,000 to 900,000 units daily for five or six weeks. The authors discussed possible reasons for the failure of the intensive course of therapy and reached the conclusion that the short duration of treatment was the principal factor. Other writers have agreed.[3,8]

However, another possibility was mentioned by King et al., namely, that the penicillin levels obtained may have exceeded the concentration which provides for optimal bactericidal effect. They refer to Eagle's preliminary report that such a paradoxical "zone" effect can be demonstrated *in vitro*. Eagle has since amplified his observations,[9,10] and there is some basis for the

[6] Hunter, T. H. The treatment of some bacterial infections of the heart and pericardium. *Bull. New York Acad. Med.*, 28: 213, 1952.

[7] Robbins, W. C. and Tompsett, R. Treatment of enterococcal endocarditis and bacteremia. *Am. J. Med.*, 10: 278, 1951.

[8] Cates, J. E. and Christie, R. V. Subacute bacterial endocarditis. *Quart. J. Med.*, 20: 93, 1951.

[9] Eagle, H. and Musselman, A. D. The rate of bactericidal action of penicillin in vitro as a function of its concentration, and its paradoxically reduced activity at high concentrations against certain organisms. *J. Exper. Med.*, 88: 99, 1948.

[10] Eagle, H. Further observations on the zone phe-

belief that this may explain failure of treatment in many of the cases under consideration. Eagle showed that when the concentration of penicillin in a medium is elevated beyond a certain zone the bactericidal effect is sharply curtailed. He found also that the diminution of the bactericidal effect of too high concentrations persists for hours after the organisms have been transferred to a medium containing quantities of antibiotic optimal for bactericidal action.

Thus these patients might not have benefited from the more conventional dosage schedule during that part of each day when the intramuscular injections were being given. Also noteworthy is the fact that the only patient whose infection was eradicated initially was the one harboring the organism most resistant to penicillin. The fact that some cases of bacterial endocarditis have required treatment with doses of penicillin as high as or higher than 14,000,000 units per day does not invalidate this hypothesis since in such cases the high dosage has only been resorted to after smaller quantities have been found ineffective, indicating considerable resistance on the part of the infecting organism. The "zone" phenomenon has generally been regarded as having little clinical significance. In the case of bacterial endocarditis, however, we are dealing with an infection in which such an effect might be anticipated because bactericidal action of the chemotherapeutic agents appears to be all-important.

It would appear, then, that we are now justified in re-opening the question of necessity for prolonged antibiotic treatment in all patients with this disease. Some tendency to shorten the average course of therapy is already evident. Reports on treatment of bacterial endocarditis from various clinics indicate that discontinuance of treatment at the end of twenty-one to thirty days is not unusual. Geraci states that fifteen selected patients, all with penicillin-sensitive organisms, were treated for only ten to fourteen days with a penicillin-dihydrostreptomycin combination and satisfactory results were obtained.[11] Review of our experience at the New Haven Hospital in the past two years, during which the penicillin-streptomycin combination was used in all cases, reveals that only two of eighteen patients were treated for as long as forty-two days, therapy being stopped in twenty-one to thirty days in fifteen, and after fourteen days in one patient. There is no record that relapse of the infection occurred in any of these patients.

It is probable that selection can be made of patients who may be expected to respond satisfactorily to treatment maintained for only two to four weeks. Two principal criteria for such classification would be short duration of illness and an infecting organism sensitive to penicillin. A further indication would be prompt clinical improvement after the inception of antibiotic treatment. Conversely, there are criteria which indicate advisability of prolonged treatment. These include: (1) Long duration of illness before beginning of therapy; it is generally agreed that when symptoms have been present for more than two to three months cure by chemotherapy is considerably more difficult. (2) Infecting organism relatively insensitive to penicillin, as in the case of enterococcus infection. (3) Patients without demonstrable bacteremia; diagnosis may be delayed in such cases, and the effect of penicillin may be impaired by the fact that colonies of bacteria are situated deep in the vegetations, inaccessible to both antibiotics and phagocytes.

The physician who accepts responsibility for management of a case of bacterial endocarditis must maintain a close follow-up for evidence of relapse, particularly during the first month or two. A relapse, while certainly not desirable, is not necessarily disastrous, as re-treatment may yet be successful. There is not much likelihood that significant alteration in penicillin-sensitivity will occur. In a disease of such gravity conservatism is certainly proper, and all would agree that any error should be in the direction of overly long treatment. Nevertheless, there are grounds for suggesting that in selected cases antibiotic therapy can safely be terminated after two to four weeks. This would mean considerable saving to the patients in terms of discomfort and expense.

PAUL B. BEESON, M.D.

nomenon in the bactericidal action of penicillin. *J. Bact.*, 62: 663, 1951.

[11] GERACI, J. E. Antibiotic therapy of bacterial endocarditis. II. Current trends in the treatment of subacute bacterial endocarditis. *Minnesota Med.*, 35: 861, 1952.

Clinical Studies

Influence of Gonadal Hormones on Protein-Lipid Relationships in Human Plasma*

ELLA M. RUSS, HOWARD A. EDER, M.D.† *and* DAVID P. BARR, M.D.
with the technical assistance of Julie Raymunt
New York, New York

EARLIER studies reported from this laboratory have emphasized the influence of sex on protein-lipid relationships in human plasma. Using the Cohn protein microfractionation method, Russ, Eder and Barr[1] have shown that normal young women have a relatively greater amount of alpha lipoprotein and a correspondingly smaller amount of beta lipoprotein than do normal young men, a distinction that is no longer apparent after the period of the menopause. This work has since been confirmed by others with electrophoretic and ultracentrifugal methods.[2–4] Jones and his associates[5] have shown that certain lipoproteins having a density of S_f 10–100 in the ultracentrifuge are in lower concentration in the plasma of young women than in that of young men.

These observations are of considerable interest because of their possible relevance to the pathogenesis of atherosclerosis, and particularly since it is generally known that in young women myocardial infarctions seldom develop.[6–8]

Investigation of the action of gonadal hormones which was begun in our laboratory in 1951 was stimulated by the previous demonstration of sex differences in the distribution of lipoproteins. It was encouraged by the report of Eilert in 1949[9] that estrogens administered to premenopausal and postmenopausal women cause reduction in both cholesterol concentration and cholesterol-phospholipid ratios of plasma. Some preliminary observations from our early studies on the influence of estrogens were published in 1952 and 1953.[10,11] The results obtained from administration of androgens have been mentioned briefly elsewhere.[12] This report is a more detailed presentation of data that have accumulated over a period of three years.

METHODS

Plasma proteins were separated by method No. 10 of Cohn and his associates[13] in which alpha lipoproteins are recovered in Fraction IV+V+VI and beta lipoproteins in Fraction I+III. Analyses for protein, cholesterol and phospholipids were made in unfractionated plasma and in Cohn fractions IV+V+VI, II, and I+III. The methods of fractionation and analyses have been described in a previous paper of this series.[1]

I. Effects of Estrogens

A. Action of Estinyl® (Ethinyl Estradiol) in Survivors of Myocardial Infarction. The first tests of the action of estrogens were made on survivors of myocardial infarction who were selected for two reasons. The group was composed chiefly of males who presumably had minimal amounts of circulating estrogens before treatment. Moreover, previous observations[14] had shown that such patients usually exhibited abnormalities in plasma protein-lipid patterns of a degree that should facilitate detection of any corrective action of the hormones.

For several reasons the estrogen, ethinyl estradiol (estinyl), was chosen for initial trial. Previous experience with its use had been considerable; it could be given by mouth; its toxic

* From the Department of Medicine, The New York Hospital-Cornell Medical Center, New York, New York. These studies have been aided by a grant from the U. S. Public Health Service, by support from the Commonwealth Fund and the Albert and Mary Lasker Foundation, and by gifts from Mrs. Katherine Lilly Conroy.

† Present address: National Heart Institute, Bethesda, Maryland.

action had been minor. A daily dose of 1.0 mg. calculated as equivalent to 10,000 rat units[15] was used routinely except as otherwise specified. Choice of this dosage was arbitrary but was based on the intention of making the first tests of action as decisive as possible. When the dose was found to be effective, it was continued with little modification in order to make subsequent observations comparable.

In Table I, the results of the use of estinyl in seven survivors of myocardial infarction have been assembled. All of the patients had had one or more myocardial infarctions.

Before treatment the plasma of all subjects exhibited significant deviations from normal protein-lipid relationships. In two of them the concentration of cholesterol in unfractionated plasma exceeded the normal range. In all the percentage of total cholesterol in Fraction IV+V+VI was lower, and that in Fraction I+III higher, than normal. There was a tendency in the group toward slightly higher than normal cholesterol-phospholipid ratios in the unfractionated plasma and in Fraction I+III.

Following the ingestion of estinyl the abnormalities in protein-lipid relationships were partially or completely corrected. The most constant and characteristic effect was a change in the distribution of cholesterol, with a higher percentage of the total in Fraction IV+V+VI. In the unfractionated plasma, reduction of the concentration of cholesterol was evident in five of the seven patients and was relatively greater than that of the phospholipids. In Fraction IV+V+VI concentrations of cholesterol and phospholipids tended to increase proportionately so that the ratios of the Fraction were not appreciably changed. In Fraction I+III, however, the diminution in the cholesterol concentration so far exceeded that of the phospholipids that the ratios were lowered and in several instances were less than unity.

In inspection of the results, it should be noted that the cholesterol-phospholipid ratios of unfractionated plasma reflect both the altered distribution of lipids and the lower ratio of Fraction I+III. Since both of these factors tend to reduce the ratio in plasma, the change in this value constitutes a good index of the effect of the hormone.

Mean values before and after hormone administration are omitted because variations in dosage, duration of treatment, and other circumstances of the experiments render invalid strict comparison of individual results. At the foot of Table I, however, mean values for young men aged eighteen to thirty-five have been included for convenient comparison with the initial values for the survivors of myocardial infarction and with those obtained following the administration of estinyl.

As previously reported[10] maximum effects of estinyl were attained approximately six weeks following the initial dose of the hormone. Thereafter, the action continued with slight variation but without significant augmentation.

The longest continuous administration of estinyl in amounts of 1.0 mg. daily was approximately six months. When the use of estinyl was continued over long periods without interruption, there was no evidence of diminution of effect, acquisition of tolerance, or of resistance to the hormone.

Changes following withdrawal of the hormone are also illustrated in the table. At first, the concentration of total cholesterol in the plasma and in Fraction I+III rose rapidly and at times exceeded the pretreatment levels. Within a period of two or three weeks, the values returned to a pattern almost identical with that seen before treatment.

Comment: The gonadal effects of the hormone were evident in all cases. Loss of sexual desire and potency were noted early; after three to four weeks, enlargement of the breasts was noticeable and impotence became complete. Usually, the patients were restless, often they were dissatisfied, and they were depressed during the periods when estinyl was administered. In a few instances, gastric distress or nausea was troublesome at the outset of treatment but subsided with its continuance.

In those patients who had experienced anginal pain before the hormonal administration was started, no consistent effect of the hormone could be established. One patient (*Joh*) had an attack of moderately severe pain accompanied by electrocardiographic evidence of myocardial infarction while the hormone was being given. Another (*Gre*) developed a fatal infarction one month after hormonal treatment had been discontinued. It is perhaps worthy of mention that none of these patients of outstandingly poor prognosis died during the long periods of administration of the hormone.

In this study interest was focused upon one group of men who had survived myocardial infarction. Oliver and Boyd[16] have recently

TABLE I

EFFECTS OF ADMINISTRATION AND WITHDRAWAL OF ESTINYL IN CASES OF MYOCARDIAL INFARCTION

Subject, Sex and Age	Date	State	Unfractionated Plasma			Fraction IV+V+VI				Fraction I+III			Remarks
			Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Cholesterol (% of total)	Phospholipids (mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio	
Gil M, 39	12/18/51	Estinyl 1.0 mg. o.d. started	300	...	....	27	8.9	...	....	274	...	....	Myocardial infarction in 1949 and in 9/51; a third infarction occurred 10/19/53, at a time when patient was receiving no hormone therapy
	1/18/52		220	312	0.71	41	18.6	91	0.45	176	196	0.93	
	1/31/52		224	309	0.72	43	19.1	107	0.40	179	181	0.99	
	2/21/52		201	279	0.72	54	27.0	114	0.47	144	147	0.98	
	3/6/52	Estinyl discontinued	179	266	0.67	50	28.6	120	0.42	124	139	0.89	
	3/20/52		280	360	0.78	39	14.0	94	0.42	237	242	0.98	
	4/4/52		300	343	0.87	26	8.9	70	0.37	273	262	1.04	
	4/17/52		278	290	0.96	30	10.9	67	0.45	242	199	1.21	
	5/1/52	Estinyl 1.0 mg. o.d. started	276	304	0.91	31	11.1	80	0.39	244	211	1.16	
	5/8/52		209	294	0.71	33	16.1	84	0.39	171	193	0.89	
	5/22/52		190	288	0.66	39	21.3	106	0.37	141	157	0.90	
	6/6/52		206	...	....	43	20.4	...	....	167	...	....	
	7/1/52		171	270	0.63	54	31.4	144	0.37	116	126	0.92	
	7/10/52	Estinyl discontinued	187	...	....	56	30.5	...	....	126	...	....	
Yat M, 49	1/24/52	No treatment	322	...	....	27	8.5	...	....	295	...	....	Myocardial infarction 6/50; thrombophlebitis with pulmonary infarcts 12/51; was receiving anticoagulants during most of period of observation
	2/1/52	Estinyl 1.0 mg. o.d. started	...	...	....	..	....	...	....	...	...	....	
	2/14/52		261	...	....	47	18.3	...	....	207	...	....	
	3/6/52		228	...	....	52	23.4	...	....	170	...	....	
	3/21/52		220	312	0.70	57	25.5	141	0.40	165	164	1.01	
	4/4/52		232	303	0.77	50	22.5	110	0.45	169	153	1.10	
	4/17/52		227	...	....	57	26.0	...	....	162	...	....	
	5/1/52		198	288	0.69	55	29.4	132	0.42	132	136	0.97	
	5/20/52		220	337	0.65	63	29.0	157	0.40	154	165	0.93	
	6/5/52		186	...	....	52	27.9	...	....	132	...	....	
	6/26/52	Estinyl discontinued	...	...	....	..	....	...	....	...	...	....	
	7/20/52		295	...	....	48	16.6	...	....	237	...	....	
	7/24/52		300	341	0.88	38	13.0	86	0.44	248	212	1.17	
	8/7/52		347	370	0.94	38	11.4	115	0.33	290	216	1.34	
	10/23/52	Estinyl 1.0 mg. o.d. started	344	389	0.89	46	13.5	124	0.37	287	270	1.06	
	11/6/52		263	310	0.85	52	19.8	110	0.47	209	196	1.07	
	11/20/52		254	282	0.90	59	23.1	134	0.44	195	166	1.17	
	12/11/52		214	307	0.70	63	30.5	146	0.43	145	147	0.99	
	1/15/53		195	290	0.67	54	28.7	134	0.40	134	147	0.91	

Gre M, 53	1/17/52	Estinyl 1.0 mg. o.d. started	202	...	....	19	9.7	...	....	171	..	....	Myocardial infarction 1/11/52; occasional glycosuria; died of a second myocardial infarction 5/22/53; was receiving no hormones at time of death
	1/30/52		236	...	....	36	15.0	...	....	201	...	....	
	2/5/52		223	...	....	41	18.9	...	....	171	...	....	
	2/14/52		216	280	0.77	39	17.8	86	0.45	176	174	1.01	
	2/20/52		193	256	0.75	43	21.6	98	0.44	154	133	1.16	
	3/27/52		184	266	0.69	54	30.1	121	0.45	122	120	1.02	
	4/10/52		181	272	0.67	58	32.4	130	0.45	120	114	1.05	
	4/24/52		176	254	0.69	51	29.9	121	0.42	119	115	1.03	
	5/8/52		190	290	0.66	54	29.8	140	0.39	128	126	1.02	
	5/22/52		173	281	0.62	50	29.6	137	0.37	120	117	1.03	
	6/5/52	Estinyl dosage reduced to 0.5 mg.	...	...	....	..	....	...	....	...	...	....	
	7/3/52		182	243	0.75	51	27.9	113	0.45	132	124	1.06	
	7/15/52		198	...	....	56	29.5	...	....	135	...	....	
	8/1/52	Estinyl dosage reduced to 0.25 mg.	...	...	....	..	....	...	....	...	...	....	
	8/14/52		180	255	0.71	54	31.6	136	0.40	117	119	0.98	
	9/11/52		205	...	....	64	30.7	...	....	144	...	....	
	9/25/52		217	296	0.73	68	31.2	155	0.44	148	138	1.07	
Sie M, 22	2/4/52	No treatment	218	250	0.87	23	10.9	53	0.43	185	166	1.11	Myocardial infarction 1/14/52; unimpaired health before coronary attack; asymptomatic during observation period
	2/20/52	Estinyl 1.0 mg. o.d started	...	...	....	..	....	...	....	...	...	....	
	3/6/52		179	...	....	54	30.5	...	....	124	...	....	
	3/20/52		172	238	0.72	54	31.8	117	0.46	114	109	1.05	
	3/26/52		223	...	....	..	....	...	....	...	...	....	
	4/3/52		239	260	0.92	63	26.7	118	0.53	168	123	1.36	
	4/24/52		223	...	....	40	18.7	...	....	170	...	....	
	6/3/52		244	231	1.06	48	20.5	91	0.53	178	143	1.24	
Spi M, 29	1/3/52	No treatment	238	270	0.88	27	11.9	72	0.38	201	160	1.26	Obesity; persistent hypertension, 180/120; myocardial infarction 12/28/51; anticoagulants from 12/28/51 to 2/12/52
	1/10/52	Estinyl 1.0 mg. o.d. started	269	271	0.99	36	13.9	66	0.54	219	171	1.28	
	1/30/52		225	280	0.80	43	19.1	101	0.43	177	166	1.07	
	2/5/52		212	299	0.71	52	25.2	113	0.46	151	158	0.96	
	2/18/52	Estinyl discontinued	219	312	0.70	55	25.4	128	0.43	158	171	0.92	
	3/6/52		234	260	0.90	38	16.1	86	0.44	197	162	1.22	
	4/10/52		234	249	0.94	35	15.5	77	0.45	186	136	1.37	
	4/24/52		222	249	0.89	32	14.3	73	0.44	185	151	1.22	
	5/8/52		242	290	0.83	28	11.3	78	0.36	212	197	1.08	
Joh M, 44	9/18/52	No treatment	262	...	....	30	12.9	...	....	193	...	....	Myocardial infarctions in 1945, 1949 and on 1/1/52; chest pain without EKG evidence of infarction; on 1/22/52 had dizziness and pulse irregularity without EKG evidence of another myocardial infarction
	1/7/52		216	270	0.80	29	14.2	63	0.46	171	161	1.06	
	1/17/52	Estinyl 1.0 mg. o.d. started	...	...	....	..	....	...	....	...	...	....	
	1/23/52		216	294	0.73	41	19.6	93	0.44	167	160	1.04	
	1/31/52		209	270	0.77	39	19.2	88	0.44	161	162	0.99	
	2/5/52		224	329	0.68	55	25.9	124	0.44	153	174	0.88	
Min M, 28	11/20/50	No treatment	228	225	1.01	23	11.9	64	0.36	171	130	1.32	Had been followed for 15 yr. as a case of chronic glomerular nephritis with nephrotic syndrome; at time of these observations showed signs of renal insufficiency but no evidence of nephrotic syndrome
	2/28/52	Estinyl 1.0 mg. o.d. started	276	262	1.05	50	18.2	89	0.56	214	142	1.51	
	3/13/52		256	...	....	65	26.6	...	....	177	...	....	
	3/27/52	Estinyl discontinued	273	380	0.72	77	29.1	179	0.43	183	166	1.10	
	4/3/52		332	...	....	76	23.5	...	....	242	...	....	
	4/30/52		290	314	0.92	43	14.9	83	0.52	238	198	1.20	
Mean: 24 normal men (aged 18–35 yr.)			197	228	0.86	49	25.2	100	0.49	142	118	1.20	

reported similar results with the use of only 0.4 mg. estinyl daily in twenty hypercholesterolemic men with coronary heart disease. They noted also that the decrease in concentration of cholesterol was entirely in the esterified fraction and that content of free cholesterol was unchanged by the hormone. In four of the seven cases in which cholesterol partitions were performed, we found that the free cholesterol decreased with the total. The average of the free to total ratios before and after was not significantly altered.

Our observations offer no information concerning the action of estinyl in women. The studies of Eilert[9,17] indicate that similar effects on cholesterol concentration and cholesterol-phospholipid ratios were obtained following the use of estinyl in both pre- and postmenopausal women.

B. Action of Estinyl (Ethinyl Estradiol) in Primary Hypercholesterolemic Xanthomatosis. In the previous group of patients, the occurrence of myocardial infarction was interpreted as clinical evidence of the presence of atherosclerosis. None of the cases, however, was an extreme example either clinically or chemically of predisposition to a deposit of lipids in the arterial walls or in other tissues. To study the effect of estinyl under circumstances in which maximum susceptibility to atheromatous disease is clinically and chemically evident, patients with primary hypercholesterolemic xanthomatosis were selected. Results of seven such cases are presented in Table II. All of them were hypercholesterolemic and exhibited in exaggerated form deviations from normal patterns of protein-lipid relationships. Six of the group gave a history of xanthomatous involvement in other members of the family. Two (*Tel* and *Gef*) had suffered attacks of myocardial infarction, and only three (*Pol*, *Sen* and *Wol*) of the seven had been entirely free of symptomatic or electrocardiographic evidence of coronary heart disease. One of the patients (*Sen*), whose case will be described later in more detail, exhibited in addition to hypercholesterolemia a degree of hyperlipemia which brought into question the correctness of his inclusion in the group of primary hypercholesterolemic xanthomatosis. It could be contended that his condition should be classified as essential hyperlipemia.

Estinyl was given to six of these patients in the same dosage as was used for the survivors of myocardial infarction. Observations were made during periods when there were no perceptible variations in the clinical state. In the seventh patient (*Tel*), 2.0 mg. daily by mouth was substituted during a short period for the routine 1.0 mg. dose. Chronic cardiac decompensation with acute episodes of myocardial infarction, thrombophlebitis and pulmonary infarction complicated the period of experimental observation. The history of this patient has been published in detail elsewhere.[18] In *Sen*, lack of cooperation led to irregularity and to some uncertainty as to the exact dosage during the first period of administration.

Following the use of estinyl there was in the group but not in all its individuals a tendency toward reduction in the concentration of cholesterol in the unfractionated plasma and in Fraction I+III. As in the group of myocardial infarctions, the most constant change following the administration of estinyl was a shift in the distribution of cholesterol, with relative increase in Fraction IV+V+VI and corresponding decrease in Fraction I+III. In general the reduction in the concentration of phospholipids in Fraction I+III and in the unfractionated plasma was less than that of cholesterol, with resulting diminution of the cholesterol-phospholipid ratios. In Fraction IV+V+VI the change in concentration of cholesterol and phospholipids was usually proportional, so that the ratios varied little from pretreatment values.

In the case of *Tel*, judgment concerning the effects of estinyl was difficult because his clinical condition during the period of observation was constantly varied by the progress of his heart disease. Even in his case, however, the effects were perceptible. The percentage of cholesterol in the form of alpha lipoprotein was substantially increased, and that in the form of beta lipoprotein was correspondingly diminished. Cholesterol-phospholipid ratio in the plasma and in Fraction I+III was lower. It is noteworthy that in this case doubling of the usual daily dosage of estinyl for a period of seventeen days resulted in no augmentation of the chemical effects of the hormone.

Comment: The expected gonadal effects upon sexual desire and potency and upon the hyperplasia of the mammary glands were notable in all patients after a few weeks of treatment. In most cases, other clinical effects of the estinyl were confined to some gastric distress and a feeling of irritability or depression accompanying the impotence. Especially in patients with heart

failure, administration of estinyl resulted in retention of salt and water. In *Tel* this may have been a factor in the deterioration of his clinical condition, and it is possible that some of his attacks of pulmonary edema could be attributed to the action of the hormone.

with precise measurements before and after treatment failed to reveal any significant differences in size. In only one patient was it possible to demonstrate that estinyl had an effect on the xanthomatous deposits.

Sen was a skilled artisan who for several months

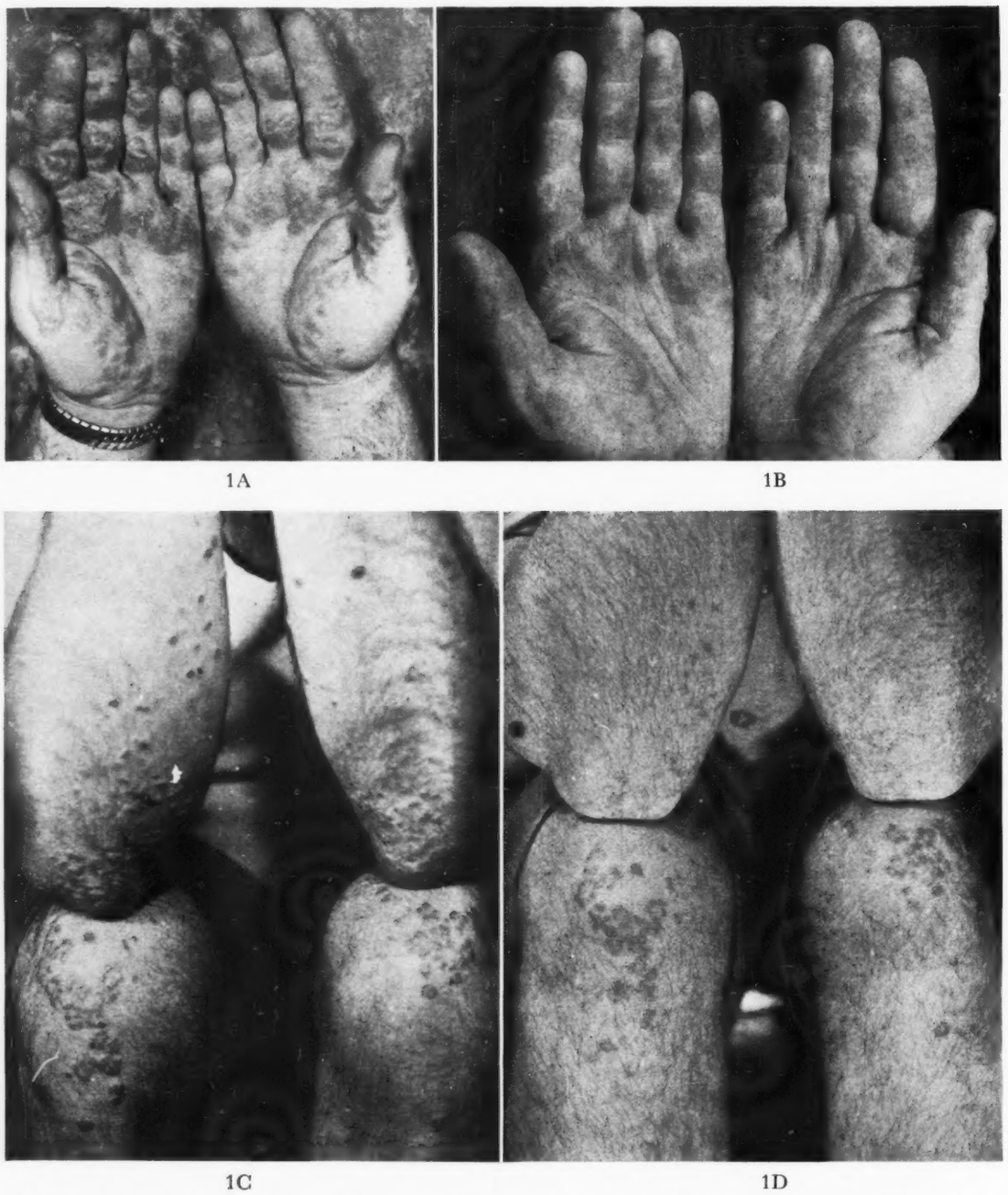
TABLE II

EFFECTS OF ADMINISTRATION AND WITHDRAWAL OF ESTINYL IN CASES OF PRIMARY HYPERCHOLESTEROLEMIC XANTHOMATOSIS

Subject, Sex and Age	Treatment		Unfractionated Plasma			Fraction IV+V+VI				Fraction I+III		
						Cholesterol						
	Amount	Time (days)	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio	(mg./100 ml.)	(% of total)	Phospholipids (mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio
Tel M, 20	None	...	623	456	1.36	18	2.9	37	0.48	589	365	1.61
	Estinyl 1.0 mg.	19	649	557	1.16	34	5.4	71	0.47	589	441	1.33
	None	34	613	434	1.41	21	3.4	41	0.51	570	354	1.60
	Estinyl 1.0 mg.	27	711	640	1.11	38	5.5	57	0.66	644	543	1.17
	Estinyl 2.0 mg.	14	666	572	1.16	39	6.0	85	0.46	610	455	1.34
	None	19	715	544	1.31	22	3.1	49	0.44	662	472	1.40
Pol M, 26	None	...	356	...	....	28	7.8	...	....	326	...	....
	Estinyl 1.0 mg.	21	332	378	0.88	36	10.9	100	0.36	291	277	1.05
	Estinyl 1.0 mg.	40	302	334	0.90	47	15.7	114	0.41	248	215	1.15
	None	14	360	341	1.05	36	10.2	80	0.46	319	254	1.25
	None	21	340	322	1.05	33	10.1	70	0.47	296	246	1.20
Hid M, 27	None	...	506	...	....	49	9.7	...	....	456	...	....
	Estinyl 1.0 mg.	7	372	...	....	51	13.6	...	....	320	...	....
	Estinyl 1.0 mg.	26	384	376	1.02	67	17.4	153	0.44	315	223	1.41
	None	21	485	371	1.30	51	10.4	113	0.45	435	259	1.67
	None	45	457	327	1.39	46	10.1	69	0.66	400	244	1.63
Bie M, 30	None	...	494	516	0.96	29	5.9	73	0.39	449	425	1.05
	None	...	461	435	1.06	29	6.2	74	0.38	431	360	1.20
	Estinyl 1.0 mg.	21	358	337	1.06	67	19.1	123	0.55	285	211	1.35
	None	28	576	...	....	40	7.1	...	....	529	...	....
Sen M, 32	None	...	496	456	1.09	35	7.1	69	0.51	464	367	1.26
	Estinyl 1.0 mg.	16	...	...	....	..	....	...	....	...	...	....
	Estinyl 0.5 mg.	23	...	...	....	..	....	...	....	...	...	....
	None	10	311	...	....	40	12.7	...	....	274	...	....
	None	41	610	525	1.16	38	6.5	84	0.45	551	392	1.40
	None	96	626	500	1.25	39	6.3	77	0.51	579	425	1.36
	None	230	597	474	1.26	35	6.0	67	0.52	550	382	1.44
	Estinyl 1.0 mg.	10	424	399	1.06	43	10.0	88	0.49	383	304	1.26
	Estinyl 1.0 mg.	35	426	464	0.92	53	12.4	130	0.41	372	321	1.16
	Estinyl 1.0 mg.	77	487	530	0.92	55	11.4	139	0.39	426	362	1.18
	None	50	504	436	1.16	37	7.2	73	0.50	468	341	1.37
Gef M, 44	None	...	378	369	1.02	21	5.5	60	0.35	354	280	1.26
	Estinyl 1.0 mg.	22	342	315	1.08	38	11.6	75	0.51	288	218	1.32
	Estinyl 1.0 mg.	38	291	338	0.86	35	12.1	95	0.36	249	216	1.16
	Estinyl 1.0 mg.	50	281	...	....	41	14.6	...	....	241	...	....
	Estinyl 1.0 mg.	85	365	440	0.83	58	16.2	148	0.39	299	258	1.16
	Estinyl 1.0 mg.	108	340	416	0.82	46	13.6	124	0.37	290	265	1.10
	None	27	500	...	....	29	5.7	77	0.38	470	373	1.26
Wol F, 48	None	...	400	...	....	37	9.2	...	....	354	...	....
	None	...	424	...	....	35	8.5	...	....	369	...	....
	Estinyl 1.0 mg.	14	322	...	....	63	19.3	...	....	259	...	....
	Estinyl 1.0 mg.	28	347	...	....	58	17.2	...	....	279	...	....
	Estinyl 1.0 mg.	57	339	...	....	67	19.8	...	....	265	...	....
	None	14	413	...	....	52	13.4	...	....	328	...	....
	None	58	416	...	....	40	9.8	...	....	362	...	....

Observations were made on the effect of estinyl on the size and extent of xanthomatous lesions. In *Pol* and *Bie*, plaster casts of lesions

had been unable to work because of painful xanthomas on his palms and the volar surfaces of his fingers. The deposits were accompanied



1A 1B

1C 1D

FIG. 1. Hands, elbows, and knees of patient *Sen* before (1A, 1C) and after (1B, 1D) treatment with estinyl.

by swelling, redness, heat and marked tenderness. He also had a few tuberous xanthomas on his elbows and knees. A single small lesion on an extensor tendon of the hand could be outlined. In some respects he differed from the other patients with xanthomatosis. The florid palmar lesions were in contrast to the sparsity of xanthomas elsewhere. There was no xanthelasma. It was noted also that his plasma was turbid, in contrast to other members of the group, and that the neutral fat of his plasma, with a value of 1,390 mg. per 100 ml., considerably exceeded the normal values obtained in our laboratory (71–335 mg. per 100 ml.).

During the first course of treatment the lesions on the hands, knees and elbows dramatically disappeared. Two weeks after he began to take estrogen the pain and swelling of his palms were improved sufficiently to permit him to resume his work. Because he was employed, some time

elapsed before he could return for examination. In the interval he suffered gastric distress which necessitated reduction in the dosage of estinyl from 1.0 to 0.5 mg. per day. He became intensely restive because of his impotence. It could not be ascertained whether he had taken the hormone regularly, but when he finally returned it was thought that he had taken 1.0 mg. of estinyl each day for thirty-eight days and 0.5 mg. daily for ten days.

Deposits in the palms, elbows and knees had disappeared, and their former locations were distinguishable only by discoloration of the skin. In Figure 1, the xanthomatous lesions of palms, elbows and knees may be seen before and after the administration of estinyl.

It is doubtful whether during his subsequent course the hormone was taken with any regularity. After three months of the prescription he was ordered to discontinue estinyl.

Return of xanthomatous lesions of the hands, elbows and knees was gradual, and nine months without treatment elapsed before the patient requested that the use of estinyl be resumed. Reinstitution of treatment was followed by prompt disappearance of the lipid deposits. The hormone was discontinued after two and one-half months. Six months later, the lesions were again present and troublesome.

It is remarkable that in this case there was such prompt disappearance of lesions, while in the others of the group the xanthomas were not obviously affected. The result is in accord with other observations that in idiopathic and acquired hyperlipemia lesions may be altered by diet and in appropriate circumstances by administration of insulin or thyroid.[19–23]

Although in *Sen*, as in other members of the group, estinyl did not accomplish complete restoration of a normal protein-lipid pattern, his clinical improvement suggests that in some instances partial chemical changes following use of the hormone may be an appropriate therapeutic goal.

C. Action of Oral Dosage of Premarin® (Estrone Sulfate) in Survivors of Myocardial Infarction. It was thought desirable to test a hormone closely resembling the natural estrogen, estrone; estrone sulfate, or premarin, was chosen for trial. It was calculated that 15 mg. of premarin contained approximately 10,000 rat units and could be regarded as approximately equivalent to 1.0 mg. of estinyl. Some of the experience with premarin in eight atherosclerotic patients is recorded in Table IIIA.

All of them had survived one or more myocardial infarctions, and two (*Noc* and *Yat*) had been subjects for observations with estinyl. *Bat* had been studied for many years as a case of myotonia congenita.

Various amounts of premarin, from 2.5 mg. to 22.5 mg. daily, were used over different periods of time. Five of the patients (*Gro*, *Lar*, *Pol*, *Kap* and *Bat*) received 15 mg. daily for significantly long periods. Because of the slight response of *Gro* to this amount, the dosage was increased to 22.5 mg. daily for a period of six weeks. In the other three cases, smaller amounts of the hormone were used.

From inspection of Table IIIA it can be seen that the action of premarin is qualitatively similar to that of estinyl. (Table I.) In the patients who received a supposedly equivalent amount of premarin, essential restoration to normal value was obtained in three (*Lar*, *Pol* and *Kap*). In *Gro*, who did not differ in any apparent way either clinically or chemically from other patients in the group, the effect of 15 mg. daily was less than had been expected. There was, however, even in this patient an increase in the relative amount of cholesterol in Fraction IV+V+VI, a corresponding diminution in Fraction I+III, and a marked decrease in the cholesterol-phospholipid ratios of Fraction I+III and in the unfractionated plasma. The later use of a larger dose of 22.5 mg. did not augment the effect.

Slight chemical changes were observed in *Gue* with 7.5 mg. premarin daily; action was demonstrable in *Noc* with 5.0 mg., but was partially lost with a dose of 2.5 mg. daily. In *Yat*, who both before and after the use of premarin was shown to be very susceptible to the action of estinyl, no response could be shown from premarin in daily doses of 2.5 or 5 mg.

Comment: The observations on *Yat* with premarin indicate that at least one individual sensitive to estinyl was unresponsive to premarin in doses that in other patients (*Gue* and *Noc*) were sufficient to provide easily demonstrable chemical change. Symptomatically, the patients seemed to tolerate premarin better than estinyl. There were fewer complaints of gastric distress, nausea and general discomfort. The gonadal effects on the breasts, sexual desire and function

TABLE III

EFFECTS OF PREMARIN IN CASES OF MYOCARDIAL INFARCTION

Subject, Sex and Age	Date	State	Unfractionated Plasma			Fraction IV+V+V				Fraction I+III		
			Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Cholesterol (% of total)	Phospholipids (mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio
						A. Oral Administration						
Gro M, 48	2/11/52	No treatment	341	324	1.05	37	11.0	69	0.54	296	212	1.40
	5/29/52	15 mg. premarin for 15 wk.	*340*	*378*	*0.90*	*58*	*16.9*	*121*	*0.48*	*281*	*248*	*1.13*
	7/10/52	22.5 mg. premarin for 6 wk.	*316*	*360*	*0.88*	*44*	*14.0*	*132*	*0.33*	*270*	*226*	*1.19*
	7/24/52	No treatment for 2 wk.	376	397	0.95	39	10.3	...	....	338	257	1.31
Lar M, 48	4/29/52	No treatment	201	218	0.92	37	19.2	79	0.47	154	144	1.07
	7/24/52	15 mg. premarin for 10 wk	*180*	*271*	*0.66*	*66*	*36.1*	*150*	*0.44*	*115*	*94*	*1.22*
	8/7/52	No treatment for 2 wk.	210	293	0.72	69	33.0	162	0.43	136	107	1.27
Noc M, 43	4/17/52	No treatment	330	353	0.93	36	10.6	99	0.36	292	220	1.33
	5/1/52	No treatment	308	...	....	32	10.5	...	....	266	...	....
	7/1/52	5 mg. premarin for 9 wk.	*240*	*327*	*0.73*	*46*	*19.2*	*125*	*0.37*	*195*	*207*	*0.94*
	7/17/52	2.5 mg. premarin for 2 wk.	*276*	*354*	*0.78*	*45*	*16.1*	*123*	*0.37*	*233*	*233*	*1.00*
	9/18/52	No treatment for 9 wk.	276	319	0.87	34	12.1	86	0.40	246	227	1.08
Gue M, 42	4/24/52	No treatment for 10 wk.	318	336	0.95	69	21.4	126	0.54	249	187	1.33
	6/12/52	5 mg. premarin for 4 days	*308*	*367*	*0.84*	*66*	*21.4*	*137*	*0.48*	*234*	*174*	*1.34*
	6/27/52	7.5 mg. premarin for 15 days	*290*	...	....	*87*	*29.5*	...	....	*204*	...	....
Yat M, 49	8/7/53	No treatment for 6 wk.	347	370	0.94	38	11.4	115	0.33	290	216	1.34
	8/28/53	2.5 mg. premarin for 3 wk.	*330*	*344*	*0.96*	*34*	*10.7*	*94*	*0.36*	*283*	*223*	*1.27*
	10/23/53	5.0 mg. premarin for 8 wk.	*344*	*389*	*0.89*	*46*	*13.5*	*124*	*0.37*	*287*	*270*	*1.06*
Pol M, 52	2/13/52	No treatment	193	231	0.84	31	15.7	73	0.42	160	144	1.11
	6/5/52	15 mg. premarin for 16 wk.	*188*	*242*	*0.78*	*70*	*37.4*	*132*	*0.53*	*115*	*123*	*0.94*
	7/11/52	No treatment for 5 wk.	234	280	0.84	32	14.1	122	0.26	188	157	1.19
Kap M, 57	3/25/52	No treatment	231	241	0.96	30	13.5	68	0.44	192	156	1.23
	4/28/52	15 mg. premarin for 5 wk.	*220*	...	....	*50*	*23.2*	...	....	*161*	...	....
	5/15/52	No treatment for 1 wk.	194	268	0.72	43	22.5	96	0.45	146	148	0.99
Bat M, 51	3/31/52	No treatment	442	402	1.10	32	7.5	60	0.54	398	326	1.22
	5/8/52	15 mg. premarin for 5 wk.	*336*	*391*	*0.86*	*44*	*12.9*	*98*	*0.44*	*294*	*280*	*1.05*
	5/22/52	No treatment for 2 wk.	390	373	1.05	25	6.4	63	0.40	363	300	1.21
						B. Single Intravenous Dose						
Noc M, 43	6/9/53	No treatment for 19 days	282	322	0.88	37	13.0	85	0.43	242	206	1.17
	6/9/53	Premarin 20 mg. intravenously	...	...	....	..	....	...	....	...	...	....
	6/10/53	Blood drawn 24 hr. after injection of premarin	254	280	0.91	28	10.9	75	0.38	230	199	1.15
	6/16/53	No treatment for 7 days	293	308	0.95	38	13.3	90	0.43	249	209	1.19
	7/1/53	No treatment for 20 days	275	266	1.03	30	11.8	88	0.43	244	197	1.24
	7/1/53	Premarin 20 mg. intravenously	...	...	....	..	....	...	....	...	...	....
	7/2/53	Blood drawn 24 hr. after injection of premarin	290	278	1.04	42	13.9	80	0.52	259	197	1.31
	7/8/53	No treatment for 7 days	290	285	1.02	35	11.9	81	0.43	256	205	1.25
Yat M, 49	6/10/53	No treatment for 40 days	354	289	1.23	44	12.5	84	0.53	307	194	1.58
	6/10/53	Premarin 15 mg. intravenously	...	...	....	..	....	..	....	...	...	....
	6/11/53	Blood drawn 24 hr. after injection of premarin	322	294	1.06	41	12.9	88	0.46	269	194	1.41
	6/23/53	No treatment for 3 days	338	306	1.10	40	11.8	96	0.42	294	209	1.41
	7/1/53	No treatment for 20 days	336	293	1.15	37	11.0	87	0.49	292	210	1.39
	7/1/53	Premarin 20 mg. intravenously	...	...	....	..	....	...	....	...	...	....
	7/2/53	Blood drawn 24 hr. after injection of premarin	372	308	1.21	45	12.0	88	0.53	324	224	1.45
	7/7/53	No treatment for 7 days	375	300	1.25	43	11.7	87	0.54	320	223	1.43
Mra M, 38	6/30/53	No treatment	306	282	1.05	37	12.0	83	0.45	269	199	1.35
	6/30/53	Premarin 20 mg. intravenously	...	...	....	..	....	...	....	...	...	....
	7/1/53	Blood drawn 24 hr. after injection of premarin	290	276	1.05	39	13.4	78	0.51	248	189	1.31
	7/6/53	No treatment for 6 days	332	292	1.12	47	14.6	92	0.51	269	200	1.35

Note: Figures in italics indicate results on days of treatment by oral administration.

were indistinguishable when equivalent doses were given.

Partial confirmation of our observations with premarin have been furnished by Marett and Vivas[24] who observed in twelve survivors of myocardial infarction significant reduction in concentration of cholesterol and total lipid following the oral administration of premarin in doses of 5 mg. (1.25 mg. four times a day). In their series, similar effects from premarin were evident in one postmenopausal woman, in two cases of mild hypertension without clinical evidence of coronary atherosclerosis, in two cases diagnosed as atherosclerosis without myocardial infarction, and in one patient with severe generalized pruritus who presented no stigmata of vascular disease.

D. Action of Intravenous Doses of Premarin (Estrone Sulfate). In three survivors of myocardial infarction, study was made of the action of a single intravenous dose of premarin. These experiments were prompted by a report of Gitman and Greenblatt[25] that by means of this procedure they were able to diminish the concentration of beta lipoproteins of the S_f 12–20 and 20–100 classes in the serum of a patient with coronary insufficiency.

Our results are shown in Table IIIB. Two of the subjects (*Noc* and *Yat*) had been treated previously with estinyl and premarin. The other patient (*Mra*) had not received any estrogen therapy. No significant changes were seen to follow injection in doses exceeding the amounts used by Gitman and Greenblatt.

Comment: It is obvious that premarin given intravenously in single doses of 15 to 20 mg. exerted no effect on the concentration or distribution of the alpha and beta lipoproteins as observed by our chemical methods of separation. It should be mentioned, however, that the criteria in our experiments and in those of Gitman and Greenblatt are quite different, and that our experiences cannot be regarded as necessarily contradictory.

E. Action of Diethylstilbestrol. The estrogen, diethylstilbestrol, was tested in three survivors of myocardial infarction for a period of one week. Starting with 1.0 mg. during the first twenty-four hours and raising the dose by 1.0 mg. each day, the total amount for eight days was 36 mg. Calculated on the basis that 1.0 mg. diethylstilbestrol is equal to 1,200 rat units, this dosage represented approximately 43,200 rat units a week, or the equivalent of approximately one-half the weekly amount used in the estinyl experiments (10,000 rat units daily). The results are shown in Table IVA.

Two of the cases (*Yat* and *Noc*) had been studied in previous experiments for the effects of the use of both estinyl and oral premarin. The third patient (*Mra*) had received intravenous premarin but had not been tested with other oral preparations.

With diethylstilbestrol, the chemical changes observed in two of the three patients (*Noc* and *Mra*) were similar to those seen following the use of estinyl and premarin. There was a decrease in the concentration of cholesterol in the plasma and in Fraction I+III, with a corresponding decrease in the cholesterol-phospholipid ratios, and an increase in the concentration and distribution of lipids in Fraction IV+V+VI, with no alteration in the cholesterol-phospholipid ratios. In these two patients, the changes were relatively large and were reversed immediately following the discontinuance of the hormone. In the case of *Yat*, the patient who had responded poorly to small doses of premarin, the influence of diethylstilbestrol was barely perceptible.

Comment: Observations with diethylstilbestrol are fewer and were carried out over a shorter period of time. They are therefore not strictly comparable to those following use of estinyl and premarin. It is apparent, however, that diethylstilbestrol produces similar changes in the protein-lipid relationships of plasma.

F. Action of Estradiol Benzoate. The effects of the oral administration of estradiol benzoate in daily doses of 1.66 mg. were studied in a male patient who was convalescent from spinal fusion in a case of tuberculous spondylitis. It was not apparent that he had any stigmata or complications of atherosclerosis.

Estrogen treatment was instituted about six weeks after the operation was performed. Throughout the course, he was treated with streptomycin, paraminosalicylic acid and nitrozide. He was entirely afebrile and asymptomatic during the period of chemical observation.

From Table IVB it may be seen that the effects of estradiol benzoate on the protein-lipid patterns were qualitatively similar to the other estrogens. The concentrations of cholesterol in the plasma and in Fraction I+III were decreased, and the percentage of cholesterol in Fraction IV+V+VI was increased. The cholesterol-phospholipid ratio of the unfractionated

TABLE IV

EFFECTS OF VARIOUS ESTROGENS IN A VARIETY OF CONDITIONS

Subject, Sex and Age	Date	State	Protein				Lipids									
			Total Protein (Kjeldahl) (gm./100 ml.)	Protein in Fractions (Biuret) (gm./100 ml.)			Unfractionated Plasma			Fraction IV+V+VI				Fraction I+III		
										Cholesterol		Phospholipids				
				IV+V+VI	II	I+III	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio	(mg./100 ml.)	(% of total)	(mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio
A. Effects of Administration and Withdrawal of Diethylstilbestrol																
Noc M, 43	10/1/53	No treatment for 3 mo.					320	300	1.11	33	10.4	79	0.42	288	211	1.37
	10/1/53	Diethylstilbestrol started					...	...	....	..	....	...	....	....	...	....
	10/8/53	Diethylstilbestrol discontinued after total dosage of 36 mg.					290	318	0.91	45	15.4	106	0.43	246	212	1.16
	10/14/53	No treatment for 6 days					336	357	0.94	48	14.5	100	0.49	280	248	1.13
	10/29/53	No treatment for 21 days					334	284	1.18	33	10.1	72	0.46	292	218	1.34
Yat M, 49	10/1/53	No treatment for 3 mo.					362	312	1.19	38	10.8	86	0.44	315	213	1.48
	10/1/53	Diethylstilbestrol started					...	...	....	..	....	...	....	...	...	....
	10/8/53	After total dosage of 36 mg.					333	333	1.00	48	13.6	97	0.49	299	224	1.33
	10/10/53	Diethylstilbestrol discontinued					324	287	1.13	43	13.5	86	0.50	272	186	1.47
	10/15/53	No treatment for 5 days					366	306	1.20	48	13.4	89	0.54	306	202	1.51
	11/5/53	No treatment for 25 days					...	...	....	..	....	...	....	...	...	....
Mra M, 38	10/7/53	No treatment for 3 mo.					274	211	1.30	37	13.9	62	0.60	226	145	1.56
	10/7/53	Diethylstilbestrol started					...	...	....	...	....	...	....	...	...	....
	10/14/53	Diethylstilbestrol discontinued after total dosage of 36 mg.					247	283	0.87	48	19.7	100	0.48	192	183	1.05
	10/20/53	No treatment for 6 days					299	300	1.00	56	15.5	70	0.80	304	212	1.43
	11/11/53	No treatment for 22 days					376	320	1.18	46	12.7	81	0.57	309	220	1.41
B. Effects of Administration of Estradiol Benzoate in Case of Tuberculous Spondylitis Convalescent Following Spinal Fusion																
Vau M, 23	2/10/53	No treatment					160	203	0.79	33	20.9	67.9	.49	120	114	1.05
	2/25/53	Estradiol benzoate 1.66 mg. o.d. started					133	160	0.83	38	29.4	75.0	.51	88	94	0.94
	3/11/53						116	153	0.76	30	25.4	58.3	.51	85	78	1.07
	3/30/53						126	175	0.72	35	28.5	78.7	.45	86	83	1.04
	4/14/53						135	175	0.77	37	28.4	79.0	.47	91	84	1.08
	5/5/53						115	170	0.68	36	31.0	81.4	.44	78	75	1.04
C. Effects of Estrogens in the Nephrotic Syndrome																
Wie M, 19	5/17/52	No treatment	3.5	...	...	...	805	649	1.25	..	....	...	....	671	506	1.33
	6/2/52	Premarin 15 mg. o.d. started	3.6	1.2	0.1	2.6	667	616	1.08	17	2.5	45	0.38	653	536	1.22
	6/12/52		3.7	1.1	0.1	2.6	622	561	1.11	19	3.0	44	0.45	605	488	1.24
	7/1/52	Premarin discontinued	3.7	1.4	0.2	2.4	702	708	0.99	24	3.4	58	0.42	676	596	1.13
			5.2	2.8	0.3	2.1	467	340	1.37	56	11.9	105	0.53	407	235	1.73
Has M, 22	3/18/54	No treatment	5.2	3.3	0.4	1.7	410	324	1.26	56	13.8	86	0.65	352	231	1.52
	4/12/54	Estinyl 1.0 mg. o.d. started														
	4/19/54		4.7	2.5	0.3	1.9	385	325	1.20	63	16.7	98	0.64	310	206	1.50
	4/26/54		4.3	2.2	0.3	2.0	402	356	1.13	58	14.3	99	0.58	345	241	1.43
	5/3/54		4.1	2.1	0.2	1.9	464	376	1.21	63	14.1	100	0.63	378	251	1.40
			3.9	1.9	0.3	1.8	428	373	1.15	53	12.2	90	0.59	378	264	1.43
	5/11/54	Estinyl discontinued														
	5/17/54		4.3	2.2	0.3	1.8	562	420	1.34	54	9.9	93	0.59	489	302	1.62
	5/24/54		...	2.2	0.2	1.7	596	440	1.35	50	8.3	90	0.55	543	316	1.72

plasma was diminished after approximately two and one-half months.

Comment: This experiment with the use of estradiol benzoate demonstrates the action of another estrogen as capable of modifying the protein-lipid relationships in plasma and offers further evidence that the effects of estrogens are not limited to survivors of myocardial infarction.

G. Action of Estrogens in the Nephrotic Syndrome. Data obtained following the use of estrogens in two patients with the nephrotic syndrome are assembled in Table IVC.

In the first patient (*Wie*) acute nephritis developed at the age of eleven. At the time of observation he had massive edema and 3+ albuminuria with slight hematuria. The blood urea nitrogen concentration was 31 mg. per 100 ml., with a urea clearance 35 per cent of normal. Separation of the lipoproteins was unsatisfactory at this time because of the difficulties which are occasionally encountered during the fractionation of nephrotic plasmas.[14] This did not, however, affect the analyses for protein and lipid concentrations of the unfractionated plasma, the values of which are listed in Table IVC, together with ratios of cholesterol to phospholipid. He received premarin in daily doses of 15 mg. for six weeks. Chemically, there was an abrupt fall in the concentration of plasma cholesterol, and the cholesterol-phospholipid ratio was progressively diminished. Protein fractionations which were satisfactory throughout this period showed little change except for a tendency toward an increase in the cholesterol concentration in Fraction IV+V+VI. Clinically, he was little affected by the treatment.

In the second patient (*Has*) acute nephritis developed at the age of fourteen and thereafter the patient continued to have albuminuria and hypertension. In January, 1954, when first examined at The New York Hospital, he was found to have a blood pressure of 170/110, with no edema. The urine contained 4+ albumin, red blood cells and casts. The concentration of blood urea nitrogen was 10 mg. per 100 ml., and the serum protein was 4.9 gm. per 100 ml., with 2.9 gm. of albumin and 2.0 gm. of globulin. The urea clearance was 68 per cent of normal.

At the time of his first plasma fractionation, estinyl (1.0 mg. o.d.) with limitation of salt intake was prescribed. Inspection of Table IVC shows that in this case the concentration of cholesterol tended to be somewhat lower, and the percentage of cholesterol in Fraction IV+V+VI slightly higher during the administration of the hormone. The cholesterol-phospholipid ratios, always high, were somewhat reduced. Discontinuance of estinyl resulted in prompt return to values more abnormal than those originally observed. Qualitatively, the changes were like those observed with the use of estinyl in the groups of survivors of myocardial infarction and in patients with primary hypercholesterolemic xanthomatosis. Quantitatively, however, they were so small that they could not be regarded as significant except in the light of previous experience in the other groups.

Much more evident were the changes in the protein values. Following the administration of estinyl there was a large reduction in the concentration of total protein which was almost entirely accounted for by a fall in the concentration of protein (presumably albumin) in Fraction IV+V+VI. After discontinuance of the hormone there was a restoration of the protein to values approximating those observed before treatment was begun. Such effects on protein concentration were not seen in any of the nonnephrotic patients following the use of estinyl.

Comment: Symptomatically, the second patient was disturbed by the medication. During the first two days he complained of nausea and experienced unusual fatigue. He vomited on one occasion and complained that he was constantly uncomfortable. His breasts became sore after he had taken the hormone for about three weeks. Since discomfort and unfavorable chemical changes were noted in the second patient and little if any chemical changes were observed in the first patient, additional experiments with estrogens in other cases of nephrosis were discouraged.

II. Effects of Androgens

A study of the effects of androgens was initiated soon after we had demonstrated sex difference in the distribution of alpha and beta lipoproteins.[1]

A. Action of Oral Administration of Methyl Testosterone. In the preliminary study of androgen effects, methyl testosterone was selected for trial not only because of the convenience of an oral preparation but also because it had been so extensively used for clinical purposes. It was realized that it might not reflect accurately the action of other forms of testosterone. It was recognized also that some adverse effects on the liver had been reported.[26]

TABLE V

EFFECTS OF ADMINISTRATION AND WITHDRAWAL OF METHYL TESTOSTERONE (M.T.) IN A VARIETY OF CONDITIONS

Subject, Sex and Age	Diagnosis	Date	State	Unfractionated Plasma			Fraction IV+V+VI				Fraction I+III		
							Cholesterol		Phospholipids				
				Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio	(mg./100 ml.)	(% of total)	(mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio
Bar M, 64	Normal	7/25/52	No treatment	212	...	....	60	28.4	...	....	152	...	....
		8/12/52	M.T. 50 mg. o.d. for 10 days	*209*	*285*	*0.73*	*37*	*18.3*	*110*	*0.35*	*168*	*167*	*1.01*
Rus F, 36	Normal	6/4/52	No treatment	157	...	....	64	40.9	...	....	93	...	....
		6/4/52	M.T. 10 mg. o.d. started	...	...	....	..	....	...	....	...	...	....
		6/22/52	M.T. discontinued after total dose of 130 mg.	...	...	....	..	....	...	....	...	...	....
		6/23/52	No treatment for 24 hr.	145	...	....	38	26.4	...	....	102	...	....
		7/15/52	No treatment for 10 days	140	...	....	45	32.0	...	....	93	...	....
Lar M, 48	Survivor infarction	11/3/52	No treatment	186	227	0.82	55	30.2	118	0.46	121	96	1.21
		11/25/52	M.T. 50 mg. o.d. for 10 days	*169*	*175*	*0.97*	*27*	*16.4*	*67*	*0.40*	*137*	*108*	*1.27*
		2/13/52	No treatment for 11 wk.	182	248	0.73	52	29.0	118	0.44	124	110	1.13
Spi M, 29	Survivor infarction	10/27/55	No treatment	253	245	1.03	58	22.6	118	0.49	199	144	1.39
		11/20/52	M.T. 5 mg. o.d. for 24 days	*236*	*203*	*0.98*	*32*	*13.6*	*72*	*0.45*	*205*	*130*	*1.57*
		12/19/52	No treatment for 29 days	201	231	0.87	43	20.2	102	0.42	161	124	1.29
Cud M, 20	Convalescent poliomyelitis	9/22/52	No treatment	169	174	0.97	35	21.5	67	0.52	128	103	1.24
		10/8/52	M.T. total dose of 450 mg. in 16 days	*167*	*176*	*0.96*	*20*	*12.1*	*57*	*0.35*	*146*	*126*	*1.20*
		12/15/52	No treatment for 66 days	162	186	0.87	40	24.9	86	0.46	117	96	1.22
Lan M, 35	Convalescent poliomyelitis	9/16/52	No treatment	195	233	0.84	55	27.9	104	0.53	139	118	1.19
		9/30/52	M.T. total dose of 400 mg. in 15 days	*177*	*170*	*1.05*	*39*	*21.6*	*77*	*0.50*	*140*	*107*	*1.30*
		10/22/52	No treatment for 20 days	203	234	0.87	48	24.0	105	0.45	147	120	1.22
Wai M, 20	Convalescent poliomyelitis	9/16/52	No treatment	180	196	0.92	47	26.1	93	0.51	134	99	1.35
		9/30/52	M.T. total dose of 400 mg. in 15 days	*165*	*194*	*0.94*	*26*	*15.9*	*57*	*0.45*	*135*	*120*	*1.13*
		10/15/52	No treatment for 13 days	204	202	1.01	45	22.0	78	0.58	160	111	1.40
Had M, 26	Convalescent poliomyelitis	9/16/52	No treatment	177	171	1.04	29	16.7	66	0.43	138	118	1.17
		9/30/52	M.T. total dose of 400 mg. in 15 days	*157*	*188*	*0.84*	*21*	*13.5*	*56*	*0.36*	*132*	*130*	*1.02*
		10/8/52	No treatment for 6 days	185	200	0.93	24	13.3	64	0.38	159	135	1.19
Jan F, 16	Afebrile tuberculosis	8/11/52	No treatment	195	...	....	30	16.0	...	....	156	...	....
		9/2/52	M.T. total dose of 850 mg. in 19 days	*163*	*212*	*0.77*	*22*	*13.1*	*61*	*0.35*	*143*	*130*	*1.10*
		9/18/52	No treatment for 16 days	148	178	0.83	32	21.5	68	0.47	117	109	1.07
Cra F, 57	Afebrile tuberculosis	8/1/52	No treatment	200	...	....	35	18.1	...	....	152	...	....
		8/18/52	M.T. 50 mg. o.d. for 17 days	*256*	*266*	*0.96*	*22*	*8.7*	*60*	*0.36*	*232*	*193*	*1.20*
		9/23/52	No treatment for 37 days	232	252	0.92	39	17.4	88	0.44	181	154	1.19
Rap F, 20	Afebrile tuberculosis	8/13/52	No treatment	218	241	0.91	40	18.9	99	0.40	169	120	1.39
		8/27/52	M.T. 50 mg. o.d. for 14 days	*188*	...	....	*25*	*13.6*	...	....	*157*	...	....
		9/9/52	No treatment for 13 days	187	204	0.92	45	23.8	88	0.51	144	118	1.21

TABLE V (*Continued*)

Subject, Sex and Age	Diagnosis	Date	State	Unfractionated Plasma			Fraction IV+V+VI				Fraction I+III		
				Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Cholesterol (% of total)	Phospholipids (mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio
Gum F, 22	Afebrile tuberculosis	8/22/52	No treatment	180	269	0.67	50	27.6	120	0.41	130	126	1.03
		9/9/52	M.T. 50 mg. o.d. for 14 days	*250*	*268*	*0.93*	*33*	*13.3*	*72*	*0.46*	*214*	*177*	*1.21*
		9/22/52	No treatment for 14 days	196	245	0.80	40	20.4	88	0.45	157	151	1.04
Bil F, 41	Endometriosis	5/2/52	No treatment	188	238	0.79	49	27.1	98	0.49	126	109	1.16
		6/26/52	T.P. 25 mg. intramuscularly, o.d. except Sat. and Sun.	*212*	*201*	*1.05*	*34*	*16.3*	*68*	*0.52*	*175*	*133*	*1.32*
			M.T. 100 mg. p.o. Sat. and Sun. for 8 wk.	...	...	....	...	....	...	....	...	...	....
		7/15/52	No treatment for 19 days	190	230	0.83	49	26.4	99	0 49	136	104	1.30
Maj F, 37	Endometriosis	6/24/52	No treatment	210	242	0.87	38	18.0	87	0.45	165	150	1.10
		7/22/52	M.T. 100 mg. o.d. for 26 days	*211*	*222*	*0.96*	*22*	*10.4*	*57*	*0.39*	*191*	*149*	*1.28*
		8/14/52	No treatment for 25 days	208	219	0.95	34	16.7	74	0.47	172	133	1.29
Haa F, 39	Endometriosis	10/14/52	No treatment	152	207	0.73	41	26.7	101	0.41	113	99	1.15
		11/11/52	M.T. 100 mg. o.d. for 22 days	*392*	*339*	*1.15*	*28*	*17.3*	*60*	*0.46*	*351*	*250*	*1.40*
			M.T. 50 mg. o.d. for 4 days	...	...	....	..	....	...	....	...	...	....
		12/16/52	No treatment for 36 days	172	201	0.86	47	28.1	97	0.49	119	108	1.01
Ruo M, 64	Aortic valvular heart disease	8/25/52	No treatment	185	271	0.68	31	16.9	71	0.44	152	136	1.11
		9/8/52	M.T. 50 mg. o.d. for 14 days	*248*	*288*	*0.86*	*24*	*10.3*	*71*	*0.34*	*209*	*207*	*1.00*
Biz F, 48	Menopause	12/1/50	No treatment	288	...	....	79	29.9	...	....	177	...	....
		12/19/50	T.P. 25 mg. intramuscularly, o.d. except Sat. and Sun.	*249*	...	....	*51*	*22.2*	...	....	*169*	...	....
			M.T. 100 mg. p.o. Sat. and Sun. for 18 days	...	...	....	..	....	...	....	...	...	....
Rob F, 55	Menopause	11/22/50	No treatment	283	...	....	48	18.4	...	....	210	...	....
		12/13/50	T.P. 25 mg. intramuscularly o.d. except Sat. and Sun.	*316*	...	....	*32*	*11.1*	...	....	*252*	....	....
			M.T. 100 mg. p.o. Sat. and Sun. for 18 days	...	...	....	..	....	...	....	...	...	....
Hoo M, 29	Hypogonadism	10/21/52	Testosterone implant 5 mo. previously	211	296	1.05	40	13.2	81	0.49	259	205	1.24
		12/2/52	M.T. 50 mg. o.d. for 41 days	*484*	*394*	*1.23*	*19*	*4.1*	*43*	*0.44*	*445*	*350*	*1.27*
		12/18/52	No treatment for 17 days	346	342	1.01	32	9.4	73	0.44	302	262	1.15
Dal M, 50	Hypogonadism	11/3/52	Testosterone implant 2 mo. previously	248	265	0.94	47	19.2	99	0.47	192	160	1.20
		11/11/52	M.T. 50 mg. o.d. for 7 days	*239*	*249*	*0.96*	*31*	*13.1*	*76*	*0.41*	*208*	*176*	*1.18*
		12/23/52	No treatment for 43 days	261	299	0.87	44	16.9	96	0.46	212	193	1.10
Rud M, 29	Hypogonadism	10/20/52	No treatment	190	220	0.86	45	23.7	104	0.43	139	106	1.31
		11/13/52	M.T. 50 mg., o.d. for 17 days	*207*	*175*	*1.18*	*23*	*11.4*	*54*	*0.43*	*181*	*121*	*1.46*

Note: Figures in italics represent results on days of treatment.

Routinely, methyl testosterone was given in daily doses of 50 mg. As with the estrogens, the choice of dose was arbitrary and was made with the hope that the amount would be sufficiently large to exert easily demonstrable chemical changes without toxic action. The dosage was varied only occasionally during the course of treatment. Random observations were made on the combined effects of testosterone propionate and methyl testosterone in three endocrine patients.

Some of the changes observed following the use of methyl testosterone have been assembled in Table v. The group of subjects included two normal individuals as well as seventeen patients with various disease states and two women with symptoms of the menopause.

The results may be simply stated. In every instance there was a change in the distribution of cholesterol in a direction opposite to that observed following the administration of estrogen. Both relative and absolute amounts of cholesterol and phospholipids in Fraction IV+V+VI were decreased, and those in Fraction I+III were correspondingly increased. In ten of the twenty-one subjects the concentration of

TABLE VI

EFFECTS OF SIMULTANEOUS ADMINISTRATION OF ESTINYL AND METHYL TESTOSTERONE

Subject, Sex and Age	Date	State	Unfractionated Plasma			Fraction IV+V+VI				Fraction I+III		
			Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio	Cholesterol (mg./100 ml.)	Cholesterol (% of total)	Phospholipids (mg./100 ml.)	C/Pl Ratic	Cholesterol (mg./100 ml.)	Phospholipids (mg./100 ml.)	C/Pl Ratio
Gil M, 39	9/8/52	No treatment for 42 days	317	374	0.85	30	9.4	85	0.36	290	281	1.03
	9/8/52	M.T. 50 mg. o.d. started	...	...	....	..	....	...	....	...	...	....
	9/22/52	Estinyl 1.0 mg. o.d. started	319	341	0.94	22	6.9	52	0.41	290	280	1.04
	10/16/52	M.T. discontinued	368	...	....	13	3.6	...	....	360	...	....
	11/6/52	Estinyl dosage reduced to 0.25 mg. o.d.	269	332	0.81	56	21.7	139	0.41	202	192	1.05
	12/18/52	Estinyl discontinued	217	315	0.69	68	31.1	158	0.43	147	149	0.99
	2/5/53	No treatment for 48 days	314	325	0.97	31	9.8	77	0.40	281	269	1.04
Noc M, 43	9/18/52	No treatment for 62 days	276	319	0.87	34	12.1	86	0.40	246	227	1.08
	9/18/52	M.T. 50 mg. o.d. started	...	...	....	..	....	...	....	...	...	....
	10/9/52	Estinyl 1.0 mg. o.d. started	318	363	0.88	13	4.1	51	0.25	291	304	0.96
	10/23/52	M.T. discontinued	366	405	0.91	19	5.3	69	0.27	338	372	0.91
	10/30/52	Estinyl dosage reduced to 0.5 mg. o.d.	304	299	1.02	28	9.1	72	0.39	276	242	1.10
	11/11/52	Estinyl discontinued	241	323	0.75	49	21.0	124	0.39	183	194	0.94
Yat M, 49	8/7/52	No treatment for 42 days	347	370	0.94	38	11.4	115	0.33	290	216	1.34
	8/7/52	Premarin 0.25 mg. o.d. started	...	...	....	..	....	...	....	...	...	....
	8/28/52	Premarin dosage increased to 0.5 mg. o.d.	330	344	0.96	34	10.7	94	0.36	283	223	1.27
	10/23/52	Premarin discontinued	344	389	0.89	46	13.5	124	0.37	287	270	1.06
		Estinyl 1.0 mg. o.d. started	...	...	....	..	....	...	....	...	...	....
	1/15/53	M.T. 50 mg. o.d. started	195	290	0.67	54	28.7	134	0.40	134	147	0.91
	2/11/53	M.T. discontinued	289	363	0.80	14	4.7	56	0.24	276	313	0.88
	4/2/53	Estinyl discontinued	186	280	0.67	46	24.8	125	0.37	139	152	0.91
	4/20/53	No treatment for 18 days	242	312	0.78	45	19.0	123	0.36	190	185	1.03
Gre M, 53	1/17/52	No treatment	202	...	....	19	9.7	...	....	171	...	....
	1/17/52	Estinyl 1.0 mg. o.d. started	...	...	....	..	....	...	....	...	...	....
	5/22/52	Estinyl dosage reduced to 0.5 mg. o.d.	173	281	0.62	50	29.6	137	0.37	120	117	1.03
	8/1/52	Estinyl dosage reduced to 0.25 mg. o.d.	194	275	0.71	66	33.1	...	....	...	...	....
	9/25/52	M.T. 50 mg. o.d. started	217	296	0.73	68	31.2	155	0.44	148	138	1.07
	10/23/52	M.T. discontinued	351	362	0.97	11	3.2	40	0.28	338	308	1.10
	12/11/52	M.T. 10 mg. o.d. started	226	278	0.81	62	27.6	146	0.42	161	140	1.14
	2/5/53	Estinyl dosage increased to 1.0 mg. o.d.	274	254	1.08	21	8.0	63	0.34	247	190	1.30
	3/12/53	Estinyl dosage reduced to 0.5 mg. o.d.	261	276	0.95	21	8.3	61	0.35	231	198	1.17
	4/9/53	M.T. dosage reduced to 5.0 mg. o.d.	248	268	0.93	19	8.0	55	0.35	222	202	1.10
	5/14/53	All hormones discontinued	221	212	1.04	32	14.5	71	0.45	187	137	1.36

cholesterol in the unfractionated plasma was augmented, and in two of them (*Haa* and *Hoo*) the increase was very great. In the remaining eleven subjects, the cholesterol concentration was slightly diminished. Nine of the patients displayed a sharp rise in the cholesterol-phospholipid ratios of plasma and of Fraction I+III following treatment. In several, there was a tendency toward a decreased ratio in Fraction IV+V+VI.

Limited observations of the three cases (*Bil*, *Rob* and *Biz*) in which testosterone propionate formed the major part of the regimen are also shown in Table V. It may be significant that the changes were in the same direction and somewhat greater than the average change observed when methyl testosterone was given alone.

Cholesterol partitions were performed on the plasma of ten patients who received testosterone. In every instance the free to total ratio was increased following the administration of the hormone. The average before treatment of 0.26, with variation between 0.23 and 0.30, may be compared with 0.33, with variation of 0.27 to 0.39 after treatment.

Comment: The action of methyl testosterone produced in normal individuals and in a variety of patients who exhibited no stigmata of circulatory disease, protein-lipid patterns that approached those found in survivors of infarction. The abnormalities in protein-lipid relationships in the plasma of survivors of myocardial infarction were even more exaggerated following the use of this hormone. No hepatic disease was noted during the course of these experiments.

III. Effects of Simultaneous Administration of Estrogens and Androgens

Since estrogens and androgens were found to produce opposite effects on the concentration and distribution of lipids in the lipoproteins of plasma, studies were undertaken to ascertain how the plasma would be affected by simultaneous administration of the two oppositely acting substances. Some of the results of four such experiments on survivors of myocardial infarction are graphically depicted in Figure 2. A more detailed summary of the data may be seen in Table VI. All of the subjects had served in previous experiments on the effects of estrogen, and for comparative purposes some of the results of these experiments are included.

In both *Gil* and *Noc* the administration of methyl testosterone exaggerated the abnormalities of their untreated state by increasing the cholesterol concentration and cholesterol-phospholipid ratio of the unfractionated plasma and by diminishing the percentage of cholesterol in Fraction IV+V+VI. Although both patients had previously responded promptly to the action of estrogens, the simultaneous administration of 1.0 mg. estinyl had no effect in modifying the action of 50 mg. of methyl testosterone. There was no reversal of the lipid values toward pretreatment levels. Upon the withdrawal of methyl testosterone and the continuation of estrogen in even smaller doses (0.25 mg. and 0.5 mg. o.d.), there was a partial re-establishment of a normal pattern. The plasma cholesterol concentrations and the cholesterol-phospholipid ratios were decreased to approximately normal ranges; and there was a marked increase in both the amount of distribution of the lipids in Fraction IV+V+VI, with a corresponding decrease in Fraction I+III. Following the withdrawal of methyl testosterone, *Gil* maintained a normal pattern for nearly six weeks on only 0.25 mg. estinyl daily.

In *Yat* and *Gre* the plan of experimentation was altered. Methyl testosterone in daily doses of 50 mg. was added without interrupting the administration of estinyl, which in the case of *Yat* was given in daily doses of 1.0 mg. for three months and in *Gre* in doses reduced from 1.0 mg. to 0.25 mg. over a period of seven months. The powerful action of methyl testosterone in counteracting the effects of estinyl is shown in *Gre*. The concentration of cholesterol was increased 134 mg. per 100 ml. and that of phospholipids 66 mg. per 100 ml. The percentage of cholesterol in Fraction IV+V+VI dropped from 31.2 to 3.2, a value which was far below the pretreatment level. Both cholesterol and phospholipid concentrations were diminished in Fraction IV+V+VI with a corresponding increase in Fraction I+III. At the same time, the plasma cholesterol-phospholipid ratio increased from 0.73 to 0.97.

When methyl testosterone was discontinued, the effects of 0.25 mg. estinyl were again evident, for the plasma cholesterol concentration was decreased by 125 mg. per 100 ml. accompanied by a fall in the cholesterol-phospholipid ratio from 0.97 to 0.81. Both cholesterol and phospholipid concentrations in Fraction IV+V+VI were markedly increased, while those in Fraction I+III were correspondingly diminished.

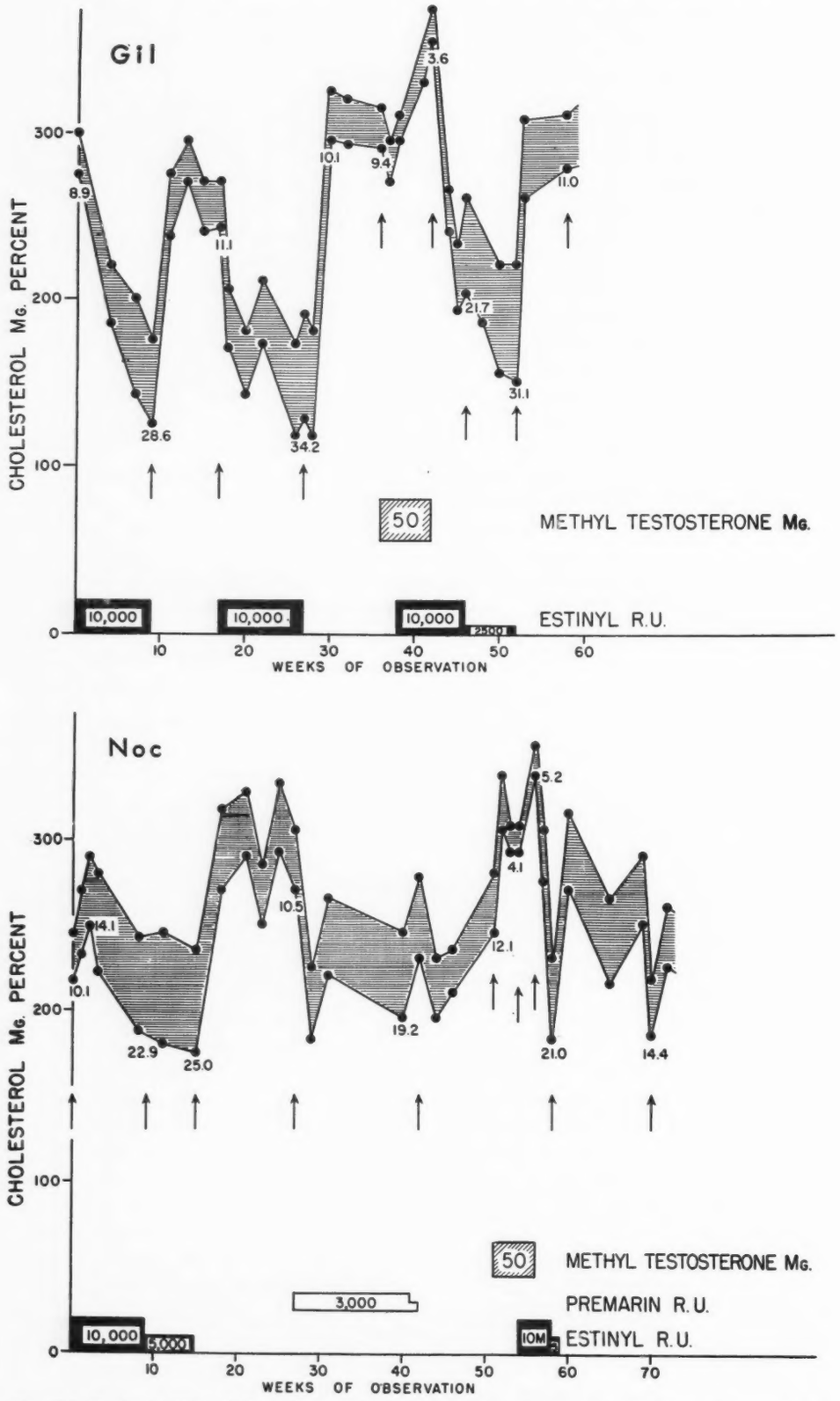


FIG. 2A. Patients *Gil* and *Noc*. Effects of estrogens and androgens in survivors of myocardial infarction (for explanation of chart construction, see legend on page 21).

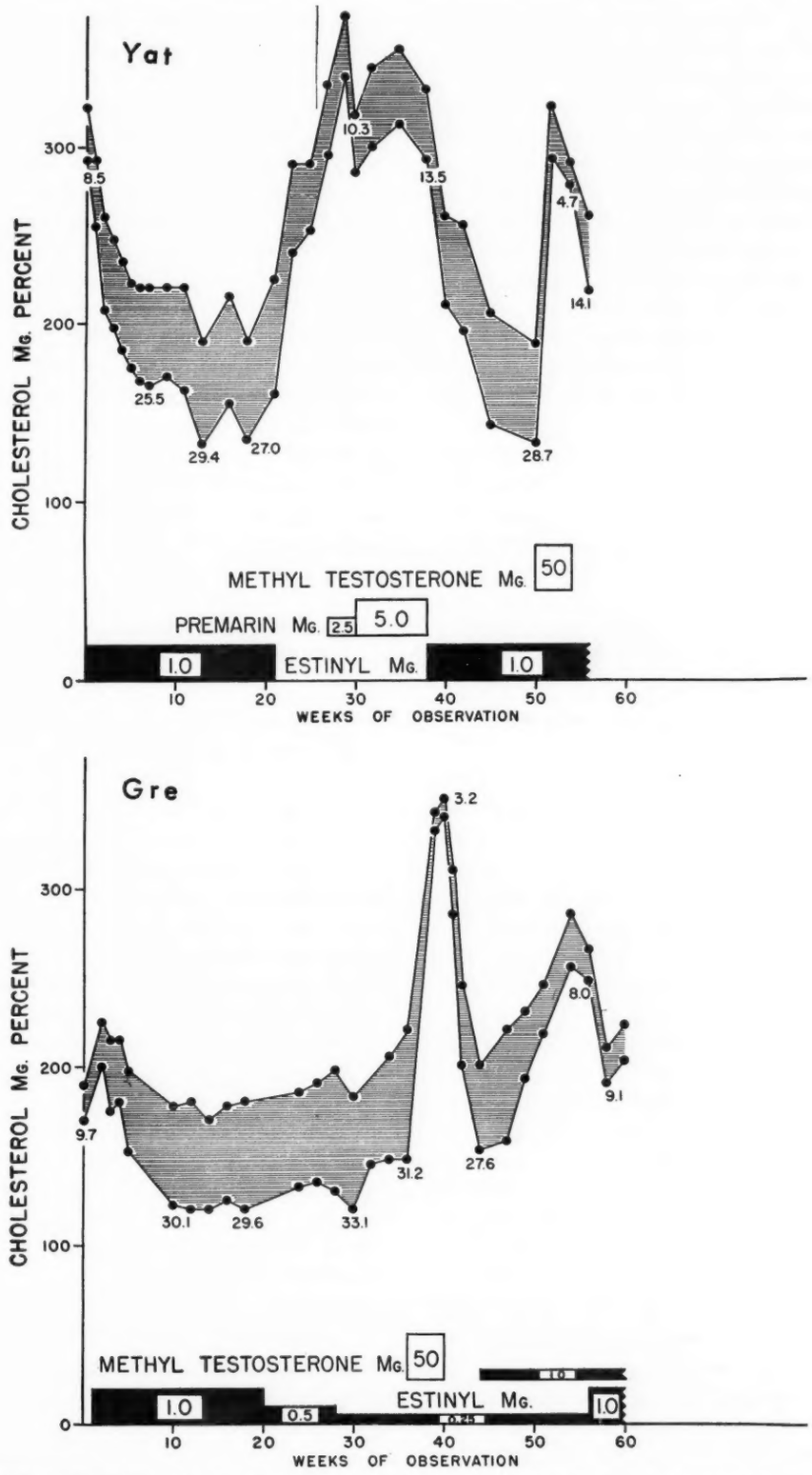


FIG. 2B. Patients *Yat* and *Gre*. Effects of estrogens and androgens in survivors of myocardial infarction. In each chart the upper limit of the shaded area represents the concentration of total plasma cholesterol; the shaded area itself, the concentration of cholesterol as alpha lipoproteins; the part below the shaded area, the concentration of cholesterol as beta lipoproteins. The figures placed immediately below the shaded area are percentages of total cholesterol as alpha lipoprotein in Fraction IV+V+VI.

The percentage distribution of cholesterol in Fraction IV+V+VI rose from 3.2 to 27.6.

Later, an experiment for the purpose of observing the effects of smaller doses of methyl testosterone after the patient had been receiving 0.25 mg. estinyl daily showed that a dose of 10 mg. per day of the androgen exerted the same qualitative effects but was quantitatively somewhat less potent than the larger doses of 50 mg. The most evident change was a rise in the cholesterol-phospholipid ratio from 0.81 to 1.08. An increase in the dosage of estinyl to 1.0 mg. a day for five weeks had little effect in reversing the action of daily doses of 10 mg. of methyl testosterone.

Finally, a reduction of the methyl testosterone from 10 to 5 mg. per day with continuation of 0.5 mg. estinyl still indicated persistence of a neutralizing effect on the action of the estrogen. Although the percentage of cholesterol in Fraction IV+V+VI was increased from 8.0 to 14.5, the cholesterol-phospholipid ratios in unfractionated plasma and in Fraction I+III were again elevated to the levels obtained during the use of 10 mg. doses of methyl testosterone.

DISCUSSION

It appears that estinyl in relatively large doses (0.5–1.0 mg. o.d.) corrects several of the abnormalities of the plasma protein-lipid patterns in survivors of myocardial infarction. Invariably, it accomplishes a change in the distribution of lipoproteins, with increase in the concentration of alpha lipoproteins of Fraction IV+V+VI and a corresponding decrease in beta lipoproteins of Fraction I+III. Usually, there is a decrease in the plasma cholesterol and phospholipid concentrations and in the cholesterol-phospholipid ratio. It also causes a considerable change in the ratio of the concentration of cholesterol and phospholipids in Fraction I+III to the extent that the values are often less than 1.00. This suggests either unusual mixtures of lipoproteins or formation of protein-lipid combinations, presumably beta lipoproteins of a composition that varies from those recovered from Fraction I+III in normal subjects.

The action of oral estrone sulfate (premarin) in survivors of myocardial infarction appears to differ little from that of equivalent amounts of oral estinyl. An exact quantitative comparison of the effects of the two hormones is not possible because the trials are not sufficiently systematic or extensive. Single intravenous doses of 15–20 mg. of estrone sulfate are apparently without effect on either the distribution or concentration of the alpha and beta lipoproteins.

Other estrogens such as estradiol benzoate and diethylstilbestrol are also capable of modifying protein-lipid relationships of plasma, and their effects are qualitatively similar to estinyl and premarin. Any estimation of the relative influence of various estrogens on the concentration and distribution of lipoproteins would necessitate more extensive and differently organized experiments. Since qualitatively the actions of all of the estrogens tried in this study are similar, it appears that they are related to estrogenic activity and are not attributable to the chemical radicles of specific compounds. Their action is also apparently not limited to survivors of myocardial infarction.

In primary hypercholesterolemic xanthomatosis which may be regarded as the most severe form of lipid disturbance predisposing to atherosclerosis, the administration of estinyl is followed by predictable changes similar to those in survivors of myocardial infarction. Frequently, there is a reduction in the cholesterol concentration of plasma; invariably, there are changes in the distribution and a tendency to lowering of cholesterol-phospholipid ratios in plasma and in the beta lipoproteins of Fraction I+III. In no instance, however, is there complete restoration of normal protein-lipid patterns. As in survivors of myocardial infarction, the chemical effects of estinyl may be maintained as long as the hormone administration is continued; they disappear abruptly when treatment is discontinued.

Chemical changes following the use of estinyl and premarin in the nephrotic syndrome are difficult to evaluate because of the extremely variable course of the condition. Our observations of their effects in two subjects offer little hope, however, that the lipid abnormalities of the syndrome can be significantly altered by the use of estrogens. Although, qualitatively, the changes are similar to those observed in survivors of myocardial infarction and in patients with primary hypercholesterolemic xanthomatosis, they are quantitatively too small to be significant. Unfavorable alterations in the protein composition of plasma following the use of estinyl in one of the subjects discouraged trial of the hormone in other cases.

Methyl testosterone modifies protein-lipid relationships in plasma in a manner opposite to

that observed following the administration of estrogens. The most constant effect is in the distribution of cholesterol and consists of a relative decrease in alpha lipoproteins in Fraction IV+V+VI and relative increase in beta lipoproteins of Fraction I+III. Other changes often noted are an increase in the cholesterol-phospholipid ratio of the unfractionated plasma, and in Fraction I+III, and, occasionally, a decrease in Fraction IV+V+VI. A drop in the plasma cholesterol concentration is unpredictable. Even small amounts can exaggerate the abnormal protein-lipid pattern of a survivor of myocardial infarction. Intramuscular doses of testosterone propionate appear to have the same if not even greater effect upon protein-lipid relationships.

The antagonistic effects of estrogens and androgens are best shown when the two hormones are administered simultaneously. It is apparent that, with the doses used in these experiments, the action of the androgen, methyl testosterone, is far more potent than that of the estrogen estinyl. Complete obliteration of the estrogenic effects may be obtained by relatively small doses of methyl testosterone. Experiments devised to show the relative potency of the hormones under a great variety of conditions would be necessary before physiologic implications could be formulated.

It is noteworthy that, in the chick, Stamler and his associates[27] were able to contrive a combined dose of estrogen and androgen which had no feminizing effect but could protect against coronary artery lesions in cholesterol-fed chicks.

Under the conditions of our experiments, the effects of methyl testosterone following or during the administration of estrogen were greater than when the testosterone was given alone. Our data are, however, insufficient to establish a potentiating effect of the estrogen. Under the conditions of combined administration the deviations from normal accomplished by the androgen are greater than those seen in any pathologic conditions except hypercholesterolemic xanthomatosis or nephrosis and must be regarded as disturbing if not alarming.

SUMMARY

The concentration and the distribution of lipids bound as lipoproteins in plasma are modified by gonadal hormones.

The ingestion of estrogen in the form of ethinyl estradiol, estrone sulfate or diethylstilbestrol tends to correct the pathologic protein-lipid relationships of survivors of myocardial infarction, and in many instances accomplishes complete restoration of normal patterns.

In primary hypercholesterolemic xanthomatosis the effect of estinyl is qualitatively similar but is not sufficient to restore normal patterns.

In two cases of nephrosis chemical changes qualitatively similar to those observed in survivors of myocardial infarction were perceptible but were so small as to be therapeutically insignificant.

Methyl testosterone exerts the opposite chemical effect. It exaggerates the chemical pathology of survivors of myocardial infarction and can produce abnormalities in plasma protein-lipid relationships of individuals whose protein-lipid patterns have been previously normal.

When the estrogenic and androgenic hormones are given simultaneously, estrogenic effects are modified or obliterated. It has not been definitely demonstrated that the actions of testosterone are modified by estrogen.

The experiments demonstrate that lipoproteins are subject to chemical manipulation but do not explain the mechanisms by which gonadal hormones operate.

These observations appear to have possible significance in the pathogenesis of atherosclerosis. They indicate a chemical reason for the relative immunity of young women to the complications of atherosclerosis. They suggest that the action of estrogenic substances in atherosclerotic persons exhibiting striking protein-lipid abnormalities might be beneficial. They suggest that the use of methyl testosterone in such patients might be detrimental.

While the observations have certain therapeutic implications, they indicate side actions which will make the use of estrogens unacceptable to many patients. It is clearly established that the administration of these hormones eliminates chemical abnormalities which may be regarded as detrimental; however, more extensive clinical studies will be necessary before estrogens can be considered useful in the prevention of atherosclerosis or in the treatment of its complications.

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The Serum Lipoprotein and Cholesterol Concentrations of Central and North Americans with Different Dietary Habits*

GEORGE V. MANN, M.D., J. ANTONIO MUÑOZ, M.D. *and* NEVIN S. SCRIMSHAW, M.D.
Boston, Massachusetts

THERE is now strong evidence to indicate that both the quantity of food habitually eaten and its quality are related to the etiology of atherosclerosis in man. Although these cannot be the only determinants in the development of the disease process, both the caloric balance as determined by body weight[1–3] and the proportion of food calories derived from fat[4–6] have been found to correlate to a significant extent with the prevalence of clinical manifestations of atherosclerosis. It would be useful to apportion the relative importance of these dietary factors among other contributing causes since these are elements of the environment which can be altered by appropriate nutritional measures.

The chronic nature of atherosclerosis, coupled with the rigidity of human dietary habits, preclude a directed experiment but human cultural groups are sufficiently diverse to supply natural material for the investigation of these problems. Such a study has been undertaken with groups of North and Central American subjects which habitually consume very different diets. The serum lipid measurements of a rural Central American group have been compared with those of both urban Guatemalans and North Americans who consume much more protein, fat and cholesterol. Striking differences in the cholesterol levels and in the serum lipid patterns have been encountered.

PROCEDURES

Selection of Subjects. The Central American subjects were of two categories. Group A included persons of predominately Mayan Indian origin and cultural characteristics residing in rural, highland villages. Careful cultural, clinical and dietary observations had previously been carried out by workers from INCAP in the majority of the villages used in this study.[7–11] The individuals were all volunteers who were given a brief physical examination which included the measurements of height, weight, blood pressure and pulse rate. Those with acute or chronic diseases, and women who were pregnant or lactating were excluded when these conditions were revealed by the examination.

Group B included persons residing in either Guatemala City or Antigua and living in a favorable economic situation. The majority of the males were physicians, army officers or other business and professional men. The women were members of the families of children attending the "Guatemalan American School" in Guatemala City, the most expensive of the private schools. All had resided at least five years in Guatemala City and the majority were native born Guatemalans. These persons were also volunteers who appeared to be in good health. Measurements of height, weight, blood pressure and pulse rate were made and pregnant and lactating women were excluded.

The North American subjects taken for comparison are referred to as Group C. These were United States business and professional men and women, and office employees who were studied at the time of an annual health protection examination given by their organizations. The group does not include low income or poorly

* From the Department of Nutrition, Harvard School of Public Health, Boston, Mass., and the Institute of Nutrition of Central America and Panama (INCAP), Guatemala City, Guatemala. The Institute of Nutrition of Central America and Panama is a cooperative activity of Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama, administered by the Pan American Sanitary Bureau, Regional Office for the Americas of the World Health Organization. This study was supported in part by grants from the National Heart Institute (No. 932-C) of the National Institutes of Health, Public Health Service, Bethesda; the American Meat Institute, Chicago; and the Albert and Mary Lasker Foundation, New York City. A portion of this work was done while the senior author was an established investigator of the American Heart Association.

nourished individuals. These subjects were examined by a physician, a medical history was taken and the blood pressure recorded. A urine sample was examined for sugar and protein, and an electrocardiogram was taken. Subjects with evidences of acute or chronic disease were eliminated from the study. Those with a blood pressure exceeding 140/90, with an abnormal or questionable electrocardiogram, with an abnormal finding in the urine examination or with a history of cardiovascular disease were also excluded from the present considerations.

Dietary Methods. The diets of the Central American subjects of Group A were evaluated by seven-day family diet surveys collected by nutritionists familiar with the language, customs and foods of those people. These surveys were carried out in three of the six communities sampled, and in two other villages in the study area. In these surveys each family was visited daily and food portions were weighed when possible. The individual nutrient intakes were estimated using a food composition table based on the analysis of Central American foods[12] and with dietary allowances modified from those of the National Research Council (U. S.) to conform with local environmental conditions and mean body weights.[13] The data shown represent the findings in a combined sample of eighty-two families which, while not always included in the serum study, are believed representative of those subjects.

Randomly selected subjects in Group B, the urban Guatemalan business and professional persons, were requested to keep a record of their individual food consumption for a period of seven days. This was supplemented with personal interrogation when the questionnaires were returned. Fifteen of the persons cooperating were women, and eight were men.

The dietary approximations of the United States subjects of Group C were representative of those described in the literature.[14,15]

Laboratory Methods. The blood samples were collected in the field in Central America. These were immediately transported to the INCAP laboratory and the serum recovered and placed in labelled tubes for transport by air to Boston. Serum samples were kept at 0–5°C. during transport. The analyses were begun three to five days after the blood was drawn. Lipoproteins were measured with the ultracentrifuge by the method of Gofman et al.[16] Cholesterol was measured by the method of Abell et al.[17] The reliability of these methods in our hands has been described.[18]

Statistical Methods. The laboratory data for each group were first considered according to sex and decade of age. Comparison of means of these groups were made after a logarithmic transformation of the measurements in order to minimize skewness of the distributions.[19] This process leads to an asymmetric distribution of the arithmetic variance about the means so that both positive and negative standard deviations are shown.

The relative weights $\left(100 \times \frac{\text{observed weight}}{\text{ideal weight}}\right)$ were computed for all subjects on which height-weight data were available. For lack of more suitable reference data, the tables of Ideal Weight of the Metropolitan Life Insurance Company[20,21] were used for both the North and Central American groups. If the "ideal weights" of the Central Americans are in fact less than those of North Americans, this procedure would tend to overestimate the leanness of those subjects and to minimize rather than accentuate the differences upon which the conclusions have been based. The analyses of covariance[22] used to make adjustments for the differences of relative weight among the groups were applied to age ranges of subjects which were shown to have rectilinear slopes of the age-serum lipid regressions.

RESULTS

The diets of the subjects of Group A were very different from those of Groups B and C. The greatest single difference appeared to be the much lower proportion of fat calories in the largely vegetarian Central American group. A summary of the dietary habits of families in the five Central American villages measured is shown in Table I. These data are to be compared with the urban Guatemalan and North American dietaries summarized in the same table. The fat content of the diets of Group A subjects was comprised almost entirely of the intrinsic fat of the corn and other vegetable foods in the diet. There was little or no free or added fat. It will be noted from Table I that the diets of Groups B and C are similar.

Summaries of the serum lipid findings for the three groups are shown in Table II for males and females, respectively. The data are grouped according to age and the transformed means and the positive and negative variances computed as

anti-logs of the transformed measurements are shown. The evaluations of the significance of observed differences of means were done with the transformed data.

A striking characteristic of the data in Table II is the low serum cholesterol levels of the rural Guatemalan subjects of Group A. This difference of cholesterol levels is the more remarkable because of the similarity of the lipoprotein levels of the three groups. When differences of the mean lipoprotein levels occurred among the groups, they were usually *increases* of the Central American levels above the North American level. This was particularly marked among the Group A females who showed elevation of all classes of lipoproteins above the North American level. The serum cholesterol levels of the business and professional groups of Guatemala and the United States were similar. In eight of the sixteen comparisons made, the lipoprotein levels of the urban Guatemalans were higher than those of age- and sex-matched North Americans. It was also of interest that there was no real difference of cholesterol levels between males and females among the rural Guatemalans of Group A.

The trends of lipoprotein levels with age were generally similar in all the groups. These showed a parabolic change with increasing age. Figure 1 illustrates these trends for the males and females, respectively.

The data were then examined for explanations of these observed differences. Since serum lipid levels have been shown to be positively correlated with relative weights in North American subjects by Dawber et al.[23] (see Walker[24]) and by Gofman and Jones,[25] it was of interest to study the relation of relative body weights to the serum lipid differences observed here. The relative weights of the Central American subjects of Group A were consistently less than those of the North Americans. (Table III.) These Central

TABLE I

DESCRIPTION OF THE STUDY GROUPS AND THEIR DIETARIES

Group	Number of Sera Analyzed		Occupation	Daily Intakes				
	Male	Female		Calories	Protein % of N.R.C. Allowance	Fat		Proportion of Calories from Fat (%)
						Animal (gm./day)	Vegetable (gm./day)	
A, rural Central Americans	112	91	Hand crafts, agriculture, household	2306*	125	13	8	8
B, urban Central Americans	92	71	Business, professional, household	2810†	141	68	43	36
C, urban United States	1,110	265	Business, professional, office workers	3250‡	134	140		40

* This intake represents 110% of requirements calculated on the basis of N.R.C. and FAO calorie recommendations for a "reference" level of activity.

† This represents 118% of the calculated calorie requirements and 117% of the protein recommended for males and 120% of the calories and 122% of the protein for females. In general these persons are much less active physically than those in Group A.

‡ It is remarkable that there are so few adequate dietary appraisals of well-nourished United States citizens. Extensive references to this kind of information may generally be traced to Department of Agriculture data on "food available for consumption." This is obviously not adequate for the present purposes but would seem to represent a correct order of magnitude.

Americans showed a downward trend of relative weight with increasing age in contrast to urban Guatemalans and North Americans whose trend of relative weight was upward with increasing age.

The covariance analysis which takes account of the third variable, relative weight, in the comparison of the two primary variables, environment and lipid levels, indicated that relative weight was of minor importance in the

TABLE II

SERUM LIPOPROTEIN AND CHOLESTEROL LEVELS OF CENTRAL AND NORTH AMERICAN SUBJECTS ACCORDING TO AGE AND SEX

(Concentrations are milligrams per 100 ml. serum; data not adjusted for body weight differences)

Age (yr.)	Group	A Rural Guatemala			B Urban Guatemala			C United States			F Ratio Significant ($p<0.05$)*	Group Mean (differing from mean of Group C)†	
		N	$\bar{x}$	S.D.	N	$\bar{x}$	S.D.	N	$\bar{x}$	S.D.			
						I. Males							
20–29	S_f12–20	13	23	+11 −7	21	26	+24 −12	51	26	+ 21 − 12	−		
	S_f35–100		38	+37 −19		71	+66 −34		40	+ 40 − 20	+	B↑	
	Cholesterol		139	+24 −21		172	+65 −47		206	+308 −124	+	A↓	
30–39	S_f12–20	34	29	+17 −11	38	35	+24 −14	230	24	+34 −16	−		
	S_f35–100		41	+43 −21		87	+102 −47		54	+60 −28	+	A↓	B↑
	Cholesterol		143	+33 −27		210	+50 −41		218	+329 −131	+	A↓	
40–49	S_f12–20	18	27	+24 −13	22	34	+22 −14	490	36	+34 −18	−		
	S_f35–100		49	+69 −29		79	+62 −35		53	+57 −28	+	B↑	
	Cholesterol		144	+49 −37		186	+51 −40		233	+357 −141	+	A↓	
50–59	S_f12–20	16	26	+23 −12	8	42	+16 −12	254	34	+32 −16	−	A↓	B↑
	S_f35–100		35	+52 −21		81	+69 −37		47	+50 −24	+	A↓	B↑
	Cholesterol		136	+41 −31		210	+37 −32		232	+356 −140	+	A↓	
						II. Females							
20–29	S_f12–20	22	30	+20 −12	20	22	+19 −11	43	21	+16 −10	+	A↑	
	S_f35–100		47	+74 −28		32	+23 −14		16	+17 −8	+	A↑	
	Cholesterol		147	+34 −28		172	+52 −39		189	+69 −51	+	A↓	
30–39	S_f12–20	15	37	+24 −14	24	29	+18 −11	51	24	+15 −10	+	A↑	
	S_f35–100		58	+57 −29		41	+48 −22		18	+32 −11	+	A↑	B↑
	Cholesterol		156	+33 −28		200	+45 −36		203	+47 −39	+	A↓	
40–49	S_f12–20	11	39	+31 −18	16	28	+17 −11	108	27	+21 −11	+	A↑	
	S_f35–100		49	+75 −29		29	+26 −13		22	+28 −12	−	A↑	
	Cholesterol		172	+35 −29		208	+47 −38		219	+48 −29	+	A↓	
50–59	S_f12–20	9	39	+26 −16	10	59	+23 −17	48	33	+20 −13	+		B↑
	S_f35–100		41	+29 −17		73	+57 −32		31	+38 −27	+	A↑	B↑
	Cholesterol		138	+67 −46		222	+41 −35		247	+61 −48	+	A↓	

* Results of a test by the F ratio of variances of the probability that the observed differences of means of the three groups are greater than would be expected from sampling theory alone.

† Analysis of the group differences by the "t" test in order to identify which means differ with a probability of 5% or less that the observed difference is sampling error. The arrow indicates the direction of the difference from the mean of Group C.

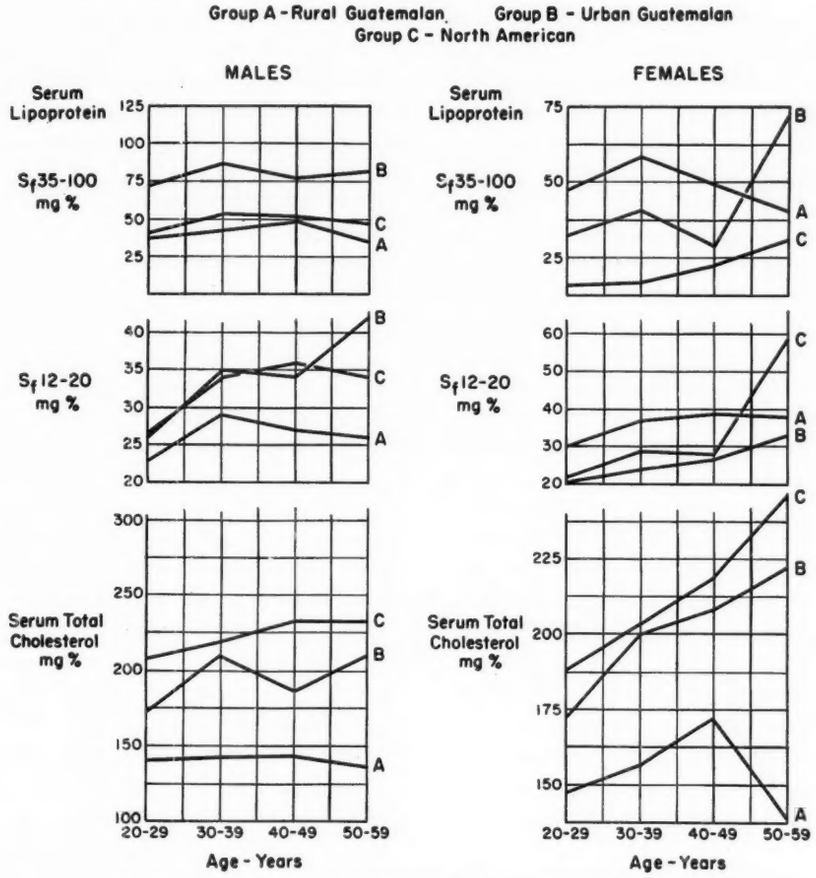

FIG. 1. A comparison of the levels of serum cholesterol and two classes of lipoproteins among subjects consuming different diets.

comparison. While the subjects of Group A, both male and female, were lighter than the age-matched subjects of either Group B or C, this fact did not greatly influence either the direction or magnitude of the observed differences of serum lipid components between the groups nor did this adjustment affect the conclusions drawn from these data.

COMMENTS

These observations indicate the presence of a distinct difference between the serum cholesterol levels of rural Guatemalan subjects and those of either urban Guatemalans or North Americans. The cholesterol levels of the rural Guatemalans are sufficiently different at all adult ages so that they would permit an accurate discrimination between the subjects using this characteristic alone. The serum beta-lipoprotein levels were in contrast to this difference for they were generally similar among all the groups and such differences as occurred were in either direction. The greater leanness of the Central Americans ap-

TABLE III

RELATIVE WEIGHTS $\left(\frac{\text{OBSERVED WEIGHT}}{\text{IDEAL WEIGHT}} \times 100\right)$ BY AGE AND SEX FOR RURAL GUATEMALANS, URBAN GUATEMALANS AND UNITED STATES SUBJECTS

Age (yr.)	Group A Rural Guatemalans $\bar{x}$	Group A Rural Guatemalans $SE_{\bar{x}}$	Group B Urban Guatemalans $\bar{x}$	Group B Urban Guatemalans $SE_{\bar{x}}$	Group C United States $\bar{x}$	Group C United States $SE_{\bar{x}}$	Group Mean (differing from mean of Group C)*
Males:							
20–29	96	± 2.77	98	± 2.84	107	± 1.82	A↓ B↓
30–39	96	± 1.54	107	± 2.19	107	± .73	A↓
40–49	93	± 1.89	109	± 2.35	110	± .45	A↓
50–59	76	± 2.00	106	± 4.95	111	± .88	A↓ B
Females:							
20–29	100	± 3.41	92	± 2.29	103	± 2.47	B↓
30–39	93	± 2.58	100	± 2.25	107	± 2.55	A↓ B↓
40–49	94	± 3192	105	± 3.75	106	± 1.55	A↓
50–59	83	± 3.33	105	± 5.38	106	± 2.53	A↓

*A↓—mean of Group A significantly < Group C ($p < 0.05$)
B↓—mean of Group B significantly < Group C ($p < 0.05$).

pears to be of minor importance in determining the low serum cholesterol levels observed in that group. On the other hand if, as is suggested in Table III by the increasing relative weights at successive ages, the urban Guatemalan and North American subjects were not in caloric equilibrium but were slowly gaining weight, a part of the observed serum cholesterol difference might be attributed to this process of "becoming fat" rather than to simply being fat. This effect of positive caloric balance has been demonstrated in short-term experiments.[3] The present cross-sectional study will not provide further information on this point.

The interpretation of the observed lipoprotein differences is more complicated because the differences were both smaller in amount and variable in direction. The S_f 12–20 lipoprotein differences were in opposite directions for males and females, the male Central Americans of Group A often showed lower levels than the North Americans but the female Central Americans showed generally higher levels. Since the serum cholesterol and lipoprotein measurements are in part representative of the same materials and since a small but real correlation between the measurements has been demonstrated,[26,27] the direction of the differences found in the male groups was expected. The difference of cholesterol levels appears disproportionately greater, however, when appraised by the standards of experience with North American subjects.[28] The measurements of female Central American subjects of Group A are unique, for they combine low cholesterol levels with high lipoprotein levels when compared with age-matched North American females.

This unusual combination is rarely seen among North American subjects. We have collected a small series of similar measurements which we call the "Blumenthal pattern" after the first subject in whom it was seen.[29] In almost 10,000 observations of human serum we have found only seventy similar patterns. The ultracentrifugal appearance of such a serum is characterized by a low main peak (S_f 0–8) with an abundance of material in the region S_f 12–100. The sera are clear and the cholesterol level is generally below 200 mg. per cent. There are no obvious common patterns of diet or clinical description among the seventy subjects with this type of sera and the Central American subjects.

Inspection of the dietary evaluations of the rural Central American subjects indicates an average caloric intake which exceeds the National Research Council allowance for persons of this weight and environment by about 10 per cent. This observation taken with the relative weight data indicating that the Central Americans of Group A were on the average 15 per cent leaner (and we have probably underestimated this leanness by the use of North American height-weight standards) than either urban Guatemalans or North Americans implies that the differences must be accounted for by larger caloric expenditures in the rural Central Americans. Consideration of the activity requirements of people in such an agrarian culture indicates this is a reasonable explanation.

After extensive studies of such people, INCAP recomendations[30] for persons in Group A include 200 more calories daily for a 55 kg. man of age 25 and 500 more calories for a 50 kg. woman of this age than are recommended by the Calorie Committee of the Food and Agriculture Organization[31] and the National Research Council (U. S.).[32] It is then possible that the magnitude of caloric turnover is an important factor in determining the lipoprotein content of blood serum. This suggestion is also logical if we accept the hypothesis which places the serum lipoproteins as a spectrum of specialized lipid-bearing proteins along which dietary lipids are passed in preparation for tissue utilization.[33]

The data of Walker et al.[3] indicated that these lipoproteins and the serum cholesterol were significantly increased by a period of positive caloric balance even when this was obtained with a very low fat dietary intake. We may suppose that a large caloric intake, even low in fat, when balanced by a large caloric expenditure might selectively increase the serum lipoproteins since these must serve the physiologic transport function. The serum cholesterol level on the other hand is determined primarily not by the type or magnitude of the intake but rather by the nature of the caloric disposal. When the excess calories are stored as fat, the cholesterol level rises; and when the calories are distributed as heat and energy, the cholesterol level is low. This or some other mechanism of semi-independent control of cholesterol and lipoprotein levels in the blood seems necessary to explain the irregular correlation of these quantities in human blood which are observed in cross-sectional studies[18] among North American subjects.

On the basis of population studies, Keys has arrived at the conclusion that serum cholesterol levels are related to the presumed dietary intake of fat.[34] The present groups were selected for study with the intent of comparing persons consuming diets of widely varying fat content. The dietary appraisals confirmed the large magnitude of the differences in fat intake. The basic question is, therefore, whether the serum lipid differences observed can be explained, wholly or partially, by this dietary difference. Although the cholesterol differences encountered are consistent with a hypothesis relating cholesterol levels to fat intake, the differences of levels observed among the groups are not so readily explained because of the marked dissociation of serum cholesterol and lipoproteins observed among rural Guatemalans. Experimental manipulation of dietary lipids in human[3,33] and laboratory animal subjects[35] has not indicated such an effect. Most other human studies have not measured both the serum cholesterol and lipoprotein levels.

It still remains to be determined whether the Central American or similar material can resolve the uncertainty of the relative importance of the serum cholesterol and the serum lipoproteins in the pathogenesis of atherosclerosis. Since the Guatemalan subjects of Groups A and B appear to offer unique advantages in studying that question, anatomic material is now being gathered.

SUMMARY

1. The total cholesterol and beta-lipoprotein measurements of the blood sera of a group of rural Central American subjects subsisting on a largely vegetarian and very low fat diet have been compared with those of urban Guatemalan and North American subjects who habitually eat large amounts of fat.

2. The rural Central American subjects, both male and female, were shown to have lower mean cholesterol levels at all ages studied than did the other groups. There was little evidence of the typical North American increase of serum cholesterol level with age among these Central Americans. There was no sex-determined difference of mean cholesterol levels by decade among the rural Central American subjects. The cholesterol levels of urban Guatemalans living in a good economic status were similar to those of North Americans.

3. The serum lipoprotein differences observed among the groups were variable. They were only slightly and irregularly lower in the rural Central American males than in the North Americans and the beta-lipoproteins of the females of this group were frequently at *higher* levels than those of the North Americans. The urban Guatemalans showed lipoprotein levels as high or higher than those of the North American group.

4. These cholesterol and lipoprotein level differences could not be explained by the greater leanness of the Central Americans although this factor could be shown to have a small effect.

5. The greater leanness of the rural Guatemalan group taken with higher caloric consumption of that group suggests that the serum lipoprotein levels may be dependent upon the magnitude of energy turnover whereas the serum cholesterol levels are increased by energy accretion or fat deposition.

6. The differences in dietary fat intake among the groups do not serve to explain the serum lipid differences because they do not permit an explanation of the dissociation of cholesterol and lipoprotein measurements which is unique in the rural Guatemalans.

7. These Guatemalan populations appear to be a useful place to evaluate the relative importance of serum beta-lipoprotein and cholesterol levels in atherogenesis.

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Analysis of 177 Cases of Hypertensive Vascular Disease with Papilledema*

One Hundred Twenty-six Patients Treated with Rice Diet

BARBARA NEWBORG, M.D. *and* WALTER KEMPNER, M.D.
Durham, North Carolina

THE prognosis in patients with hypertensive vascular disease and papilledema has always been grave. Until 1944[1,2] there was no medical treatment for this condition; since then a number of cases of malignant hypertension treated successfully with the rice diet have been reported.[3–15]

The purpose of this paper is to describe the clinical course of this disease as seen in 177 patients (treated and untreated) examined between October, 1942, and October, 1953, on our service. This series includes every patient with hypertensive vascular disease admitted during this period in whom the presence of neuroretinopathy was confirmed by fundus photographs. (Patients with chronic nephritis, i.e., history of albuminuria preceding hypertension, and polycystic kidney disease are not included.)

An attempt was made to treat all these patients with the rice diet. However, of these patients eighteen never actually took the rice diet. Sixteen of the eighteen are known to have died; in one no follow-up information is available. Only one of these eighteen patients, E. B., who was treated intermittently over a five and one-half months' period, is still living, nine years after she was first seen here. The clinical course in these patients was similar to that described by Wagener and Keith.[16] In their series of 146 patients with malignant hypertension without any special therapy only one survived five years and 79 per cent died within the first year after examination.

Thirty-three patients were willing to take the rice diet but this treatment had to be discontinued because they were unable to retain sodium or, in some cases, chloride in the serum when subjected to severe dietary restriction (less than 150 mg. sodium, less than 200 mg. chloride daily).

The rice diet was given for varying lengths of time to 126 patients. In three of these patients the follow-up information is incomplete and in three the follow-up period is too short, since treatment was started within the past year (these three are doing well). This leaves a total of 120 patients with malignant hypertension who were treated with the rice diet and in whom the effect of the rice diet on malignant hypertension can be studied. Fifty-two of these 120 patients are living.

Most of these patients, after an initial period usually of two to four months on the "basic" rice diet, received a "modified" rice diet which included small amounts of potato, cereals, non-leguminous and leguminous vegetables, meat, et cetera. In patients who continued under supervision the diet was increasingly liberalized as improvement permitted. Other patients discontinued the diet at various stages of treatment, but most of them continued to follow a salt-poor, fat-poor diet.

The urinary excretion of chloride, calculated as NaCl, on the basic rice diet, except in patients who are losing edema or who are acute or chronic salt losers) should be 5 to 15 mg. per 100 cc. urine (determined in a twenty-four-hour urine collection) if properly adhered to; on the "modified" rice diet, if correctly followed, it should be 15 to 25 mg. The chloride excretion in the urine therefore is a guide to whether or not the diet is being followed correctly.

Three of the 120 patients were between twenty and twenty-nine years of age, seventeen be-

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tween thirty and thirty-nine, fifty between forty and forty-nine, thirty-eight between fifty and fifty-nine, twelve between sixty and sixty-nine when the treatment was started. Of the fifty-two patients who are living two were between twenty and twenty-nine when the rice diet was started, five between thirty and thirty-nine, twenty-three between forty and forty-nine, sixteen between fifty and fifty-nine and six between sixty and sixty-nine. In our series age was not a significant factor in prognosis.

TABLE I
TOTAL PSP EXCRETION IN TWO HOURS AND SURVIVAL*

Total PSP Excretion in 2 Hours (%)	Number of Patients	Number Dead	Survived	
			Over 6 Months	Over 1 Year
Not done	1	1	0	0
0–15	15	15	1	0
16–25	7	7	0	0
26–35	8	8	0	0
36–45	1	1	0	0
Above 46	1	1	0	0
	33	33	1	0

* 33 patients: NaCl or Cl added to diet.

RENAL AND ELECTROLYTE STATUS

The two most important factors influencing the effectiveness of the rice diet in the treatment of malignant hypertension are the renal status (especially since salt-losing often precludes the use of the diet in patients with advanced renal involvement) and the length of time the patient is willing to adhere rigidly to treatment.

In Tables I to IV the survival times of the 120 patients treated with the rice diet and of the thirty-three patients to whom supplementary NaCl or Cl was given are correlated with the renal function and ability to conserve electrolytes: (1) Total PSP excretion in two hours (Tables I and II); (2) blood non-protein nitrogen concentration (Tables III and IV); (3) inability to maintain adequate sodium and/or chloride levels in the serum on the rice diet. (Tables I and III.)

Tables I and III list the thirty-three patients in whom drastic salt restriction was not carried out because of inability to conserve sodium and/or chloride in the serum. Tables II and IV list the 120 patients who were treated with the rice diet.

In Tables I and II the patients in both groups are listed according to the PSP excretion at the beginning of treatment. There were five patients who were critically ill in whom the PSP was not determined; all died in less than one year. There were twenty-eight patients with a total PSP excretion, in two hours, between 0 and 15 per cent. Twenty-six of the twenty-eight died in less than one year and none survived twenty-five months. Fifteen were salt losers receiving salt and thirteen were not, but with a total PSP excretion below 15 per cent in two hours the prognosis is nearly as bad in patients who do not lose salt as in those who do.

There were forty-seven patients in whom the total PSP excretion was between 16 and 35 per

TABLE II
TOTAL PSP EXCRETION IN TWO HOURS AND SURVIVAL*

Total PSP Excretion in 2 Hours (%)	Number of Patients	Number Dead	Survived One Year		Patients Living		
			Number	(%)	Number	(%)	Years (average)
Not done	4	4	0	0	0	0	...
0–15	13	13	2	15	0	0	...
16–35	32	21	19	59	11	34	3
36–55	34	19	26	76	15	44	4½
Above 56	37	11	34	92	26	70	5
	120	68	81	67	52	43	4

* 120 patients treated with rice diet.

cent in two hours. Nineteen (40 per cent) of the forty-seven patients survived one year; eleven (23 per cent) are still living with an average survival time, so far, of three years. Fifteen of the patients in this group were salt losers and received salt; all of them died.

There were thirty-five patients with a total PSP excretion between 36 and 55 per cent in two hours. Only one patient was a salt loser and received salt. Twenty-six (74 per cent) of the thirty-five patients survived one year; fifteen (43 per cent) are still living with an average survival time, so far, of four and one-half years.

There were thirty-eight patients with a total PSP excretion in two hours of 56 per cent or more. Only one patient was a salt loser and received salt. Thirty-four (89 per cent) survived one year; twenty-six (68 per cent) are still living with an average survival time, so far, of five years.

In Tables III and IV the patients in both groups are listed according to the initial non-protein nitrogen concentration in the blood. The non-protein nitrogen was over 60 mg. per 100 cc. of blood in thirty-seven patients. Twenty of the thirty-seven patients were salt losers and received salt; all twenty died. Of the seventeen who were treated with the rice diet, only three survived one year and only one (initial non-protein nitrogen 75 mg. per 100 cc. of blood; total PSP excretion in two hours 20 per cent) is still living four and one-half years after the start of treatment.

In eighty-seven patients the non-protein nitrogen was between 35 and 59 mg. per 100 cc. of blood. Twelve of these patients were salt losers and received salt; all twelve died. Seventy-five were treated with the rice diet. Fifty-five (63 per cent) of the eighty-seven patients survived one year; thirty-seven (43 per cent) are still living with an average survival time of four years.

TABLE III
INITIAL BLOOD NPN LEVEL AND SURVIVAL*

NPN (mg. per 100 cc. of blood) (Range)	Number of Patients	Number Dead	Survived	
			Over 6 Months	Over 1 Year
Over 100	6	6	0	0
75 to 99	6	6	0	0
60 to 74	8	8	0	0
50 to 59	3	3	0	0
35 to 49	9	9	1	0
Below 35	1	1	0	0
	33	33	1	0

* 33 patients: NaCl or Cl added to diet.

In twenty-nine patients the non-protein nitrogen was below 35 mg. per 100 cc. of blood. One patient was a salt loser and received salt. Twenty-three (79 per cent) of the twenty-nine patients survived one year; fourteen (48 per cent) are still living with an average survival time so far of four years.

The thirty-three patients who developed severe electrolyte imbalance are listed in Tables

TABLE IV
INITIAL BLOOD NPN LEVEL AND SURVIVAL*

NPN (mg. per 100 cc. of blood) (Range)	Number of Patients	Number Dead	Survived One Year		Patients Living		
			Number	(%)	Number	(%)	Years (average)
Over 100	4	4	0	0	0	0	...
75–100	5	4	1	20	1	20	4½
60–74	8	8	2	25	0	0	...
50–59	12	6	8	67	6	50	4½
35–49	63	32	47	76	31	49	4
Below 35	28	14	23	82	14	50	4
	120	68	81	67	52	43	4

* 120 patients treated with rice diet.

I and III; in these patients the rice diet treatment was discontinued. Development of marked electrolyte disturbance during drastic sodium and chloride restriction is a most ominous sign. Sodium chloride was given to fourteen during the first month of treatment, to seven during the second month and to seven during the third month. Five received chloride as NH_4Cl, KCl or HCl during the second to seventh week. All thirty-three patients died; twenty-seven died in Duke Hospital after an average of seventy-one days, and the other six died shortly after returning home (one to four months after first being seen in our clinic). In general, the likelihood of electrolyte loss on the rice diet is greater in patients with a low PSP excretion and/or marked azotemia. However, the inability to conserve electrolytes may, in some instances, be the chief manifestation of renal dysfunction and may occur in the absence of severe impairment of PSP excretion or of marked azotemia.

In contrast to surgical measures,[17–20] which are contraindicated when there is nitrogen retention or even moderate renal impairment (PSP excretion in the first fifteen minutes below 15 to 20 per cent), advanced renal impairment does not preclude an attempt at treatment with the rice diet and such treatment is not dangerous if the electrolyte balance can be controlled. The criteria for selection of patients for drug therapy have not yet been worked out; renal impairment, advanced age, cerebral and coronary artery involvement may under certain circumstances[21,22] contraindicate the use of hypotensive drugs; they do not contraindicate the use of the rice diet. However, Tables I to IV indicate that far advanced renal impairment seriously diminishes the chances of successful treatment with the rice diet, as with other forms of treatment of malignant hypertension.

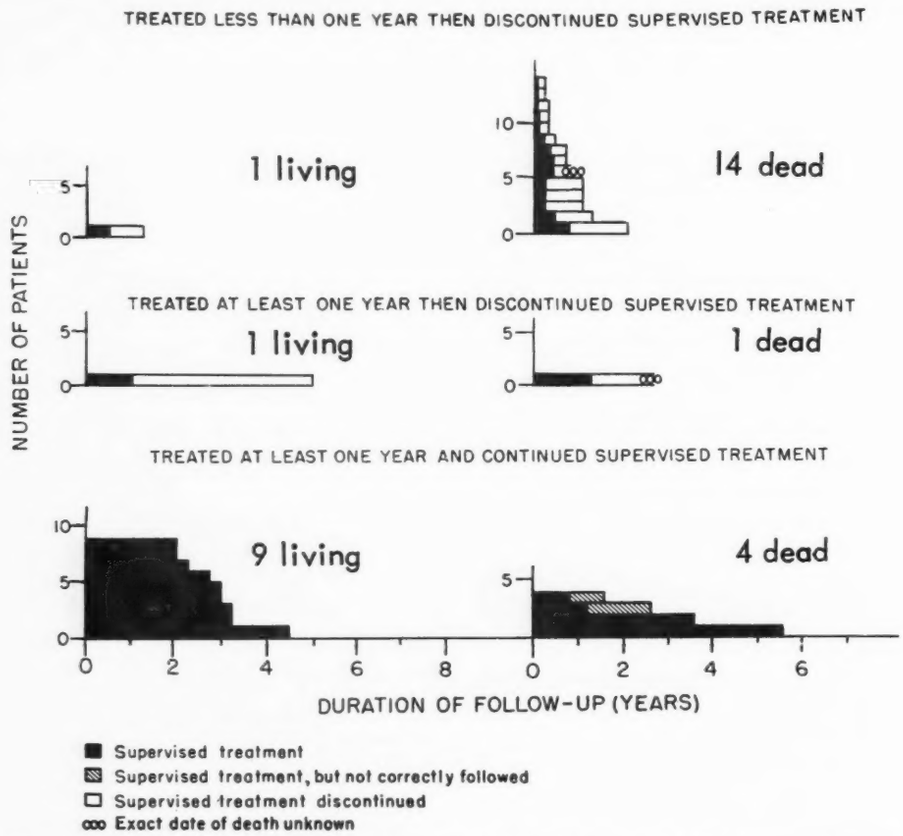

TREATED LESS THAN ONE YEAR THEN DISCONTINUED SUPERVISED TREATMENT
1 living
14 dead
TREATED AT LEAST ONE YEAR THEN DISCONTINUED SUPERVISED TREATMENT
1 living
1 dead
TREATED AT LEAST ONE YEAR AND CONTINUED SUPERVISED TREATMENT
9 living
4 dead
NUMBER OF PATIENTS
DURATION OF FOLLOW-UP (YEARS)
Supervised treatment
Supervised treatment, but not correctly followed
Supervised treatment discontinued
Exact date of death unknown

FIG. 1. Survival time and period of treatment (thirty patients, total PSP excretion in two hours, 35 per cent or less). Living, eleven patients; dead, nineteen patients.

TIME FACTOR

Since 1944[1] it has been known that the malignant phase of hypertensive vascular disease can be reversed by the rice diet; occasionally we have seen papilledema disappear within as short a time as one month, and six months of treatment with the rice diet is usually enough to cause

malignant hypertension either to revert to "benign" essential hypertension or to disappear completely.

However, the period of treatment required for modification of the underlying vascular disease and the degree to which it can be modified are more variable. In patients with the most severe involvement, uninterrupted maximal dietary treatment (as checked by a chloride excretion below 15 mg., expressed as NaCl, per 100 cc. of urine) may be necessary for years or in some cases perhaps indefinitely to maintain improvement. On the other hand, one patient, age twenty, had a normal blood pressure after two months on the rice diet, and her blood pressure is still normal five and one-half years after she had had malignant hypertension, although for the past three years she has been on a normal diet.

In Table v and Figures 1 and 2 the survival times are given according to the duration of treatment. With one exception (a patient who followed the diet poorly and died within eighteen months after first being seen in our clinic), the malignant phase of the disease had disappeared within one year in all patients treated for that length of time. The subsequent course of these patients was influenced by the severity of the underlying cardiovascular renal disease and the intensity and duration of treatment. In some patients improvement has been continuous; in others the vascular disease has remained stationary; in others it has progressed and cardiac or renal failure, coronary or cerebral artery disease or other complications have caused death. The data on the present status of the patients are given here but it is not within the scope of this paper to discuss the effect of rice diet therapy on the course of hypertensive vascular disease except when it is in the malignant phase.

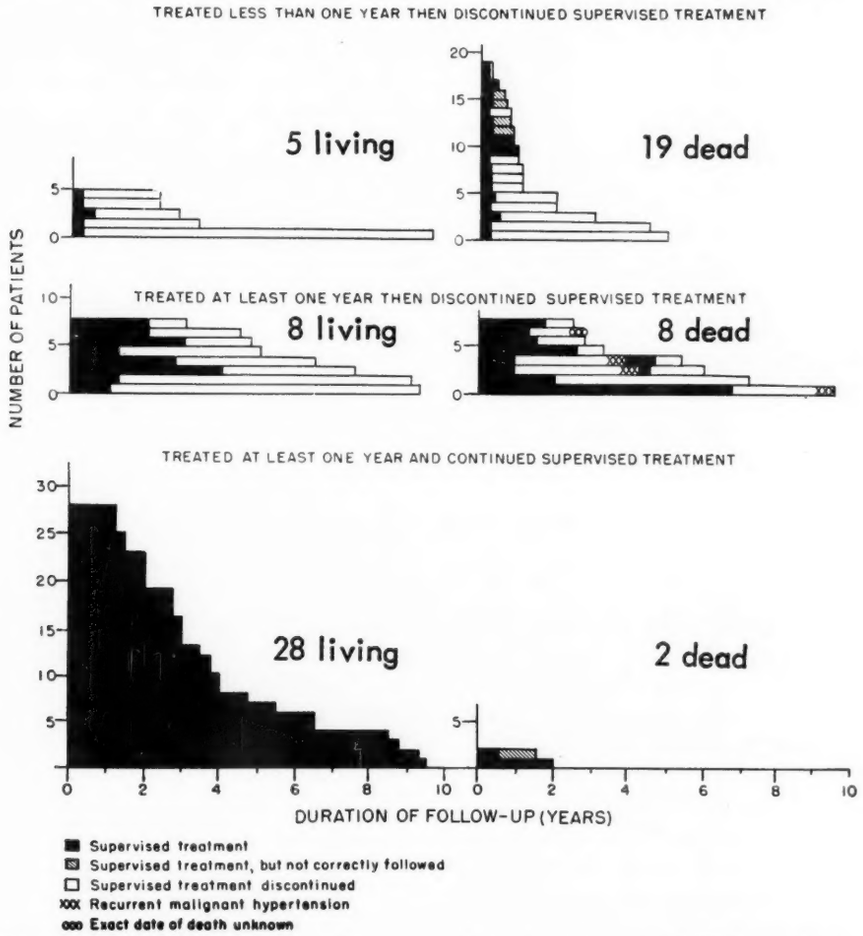

TREATED LESS THAN ONE YEAR THEN DISCONTINUED SUPERVISED TREATMENT
5 living
19 dead
TREATED AT LEAST ONE YEAR THEN DISCONTINED SUPERVISED TREATMENT
8 living
8 dead
TREATED AT LEAST ONE YEAR AND CONTINUED SUPERVISED TREATMENT
28 living
2 dead
NUMBER OF PATIENTS
DURATION OF FOLLOW-UP (YEARS)
Supervised treatment
Supervised treatment, but not correctly followed
Supervised treatment discontinued
Recurrent malignant hypertension
Exact date of death unknown

FIG. 2. Survival time and period of treatment (seventy patients, total PSP excretion in two hours, 36 per cent or more). Living, forty-one patients; dead, twenty-nine patients.

There were one hundred patients (Table v)

who were treated with the rice diet and were followed after the initial period of treatment; in these patients the relation of the length of time of supervised treatment to the survival time could be studied. (The eighteen patients who died in Duke Hospital during the initial period of treatment and two patients in whom the PSP was not determined are omitted.)

In thirty-nine of the one hundred patients, the period of supervised treatment was two to twelve months. Seven of the thirty-nine died during this period while supposedly still following the diet; only three of the seven were following it correctly. Thirty-two of the thirty-nine were treated for two to twelve months, and then to a greater or lesser extent discontinued the treatment; only six (19 per cent) of the thirty-two are still living.

Eighteen of the one hundred patients were treated one to seven and one-half, average three, years and then to a greater or lesser extent discontinued the treatment. Nine of these (50 per cent) are still living. In three instances malignant hypertension recurred two and one-half to three and one-half years after discontinuing treatment, and in two of the three papilledema again disappeared during a second period of treatment with the rice diet, which was again discontinued; in one the malignant phase could not be reversed a second time; all three died. The nine who are living had been treated with the rice diet, strict and modified, for an average of three years before discontinuing it; they have survived an average of four years since they discontinued the diet. Two are being treated elsewhere for heart failure, five have continued on a "salt-poor, fat-poor" diet; two have resumed a general diet.

Forty-three of the one hundred patients continued treatment with the rice diet; they have been treated one to nine and one-half, average four years. Thirty-seven (86 per cent) of these are still living; of the six who died, only three were following the diet correctly.

Since, as has already been indicated, there is a marked difference in survival of patients with a total PSP excretion below 35 per cent in two hours as compared to those with a total PSP excretion of 36 per cent or more in two hours, the effect of the time factor was studied in these two groups of patients separately.

Thirty (Figure 1) of the one hundred patients had a PSP excretion (in two hours) below 35 per cent. Fifteen of these patients were treated six months or less. Eight died within the first year; six died after one to two, average one and one-half years; one is still living one year after treatment was started.

Two patients discontinued treatment after one and one-half and two and one-half years, respectively; the first one died shortly thereafter; the other is still living two and one-half years after discontinuing supervised treatment. Thirteen have continued treatment from one to five and one-half, average three years; nine (69 per cent) are still living. Of the four who died while supposedly still following the diet, two were following it well as shown by a chloride

TABLE V

RELATION OF LENGTH OF TIME OF SUPERVISED TREATMENT WITH RICE DIET TO SURVIVAL*

Time of Supervised Treatment	Number of Patients	Survived One Year		Patients Living		
		Number	%	Number	%	Years (average)
Less than 1 year	39†	20	51	6	15	3
Over one year:						
Supervised treatment discontinued (after 1 to 7½, average 3 years)	18	18	100	9	50	4
Supervised treatment continued (1 to 9½, average 4 years)	43‡	43	100	37	83	4

* 100 patients treated with rice diet.

† Seven of these patients died while supposedly following the rice diet; only three of the seven were following the diet correctly.

‡ Of the six patients who died after the first year of treatment, only three were following the diet correctly.

excretion, expressed as NaCl, usually below 25 mg. per 100 cc. of urine (as compared to 5 to 15 mg. on the basic and 15 to 25 mg. on the correctly followed "modified" rice diet); two adhered to the diet poorly, chloride excretion 44 mg. per 100 cc. of urine, average of the last five determinations in each of the patients. The nine who are still alive do not at all times follow the diet correctly; the average chloride excretion in the urine has been 25 to 40, average 32 mg. per 100 cc. (average of the last five to fifteen determinations in each instance). These patients continue to return here for examination and, if indicated, for short periods of strict treatment several times a year.

Seventy patients (Figure 2) had a total PSP excretion of 36 per cent or more in two hours. In twenty-four the period of controlled treatment under our supervision was less than one year. Seven of the twenty-four died while supposedly still on the diet after six to nine, average seven and one-half months of dietary treatment; three were following the diet well (chloride excretion usually below 25 mg. per 100 cc. of urine); two were following the diet moderately well (chloride excretion 36 mg. per 100 cc. of urine, average of the last three determinations in each instance); one was not adhering well to the diet (chloride excretion 53 mg. per 100 cc. of urine, average of the last five determinations); one had been given small amounts of toast and other additions to increase the salt content of the diet during the fourth month of treatment when electrolyte imbalance developed. The other seventeen patients in this group were treated less than six months; thirteen survived one year and five are still living (three years average after first being seen at our clinic).

In forty-six patients the period of controlled treatment under our supervision was at least one year. Sixteen discontinued the diet after one to seven and one-half years: eight have died; eight are still living.

Thirty continued to follow the rice diet, strict and modified: twenty-eight (93 per cent) are still living, one to nine and one-half, average four, years after first being seen here. Two died while supposedly still on the diet: one was following the diet well (chloride excretion usually below 20 mg. per 100 cc. of urine), the other was following the diet only moderately well (chloride excretion 35 mg., average of ten determinations).

TABLE VI

RETINOPATHY IN 100 PATIENTS TREATED WITH RICE DIET*

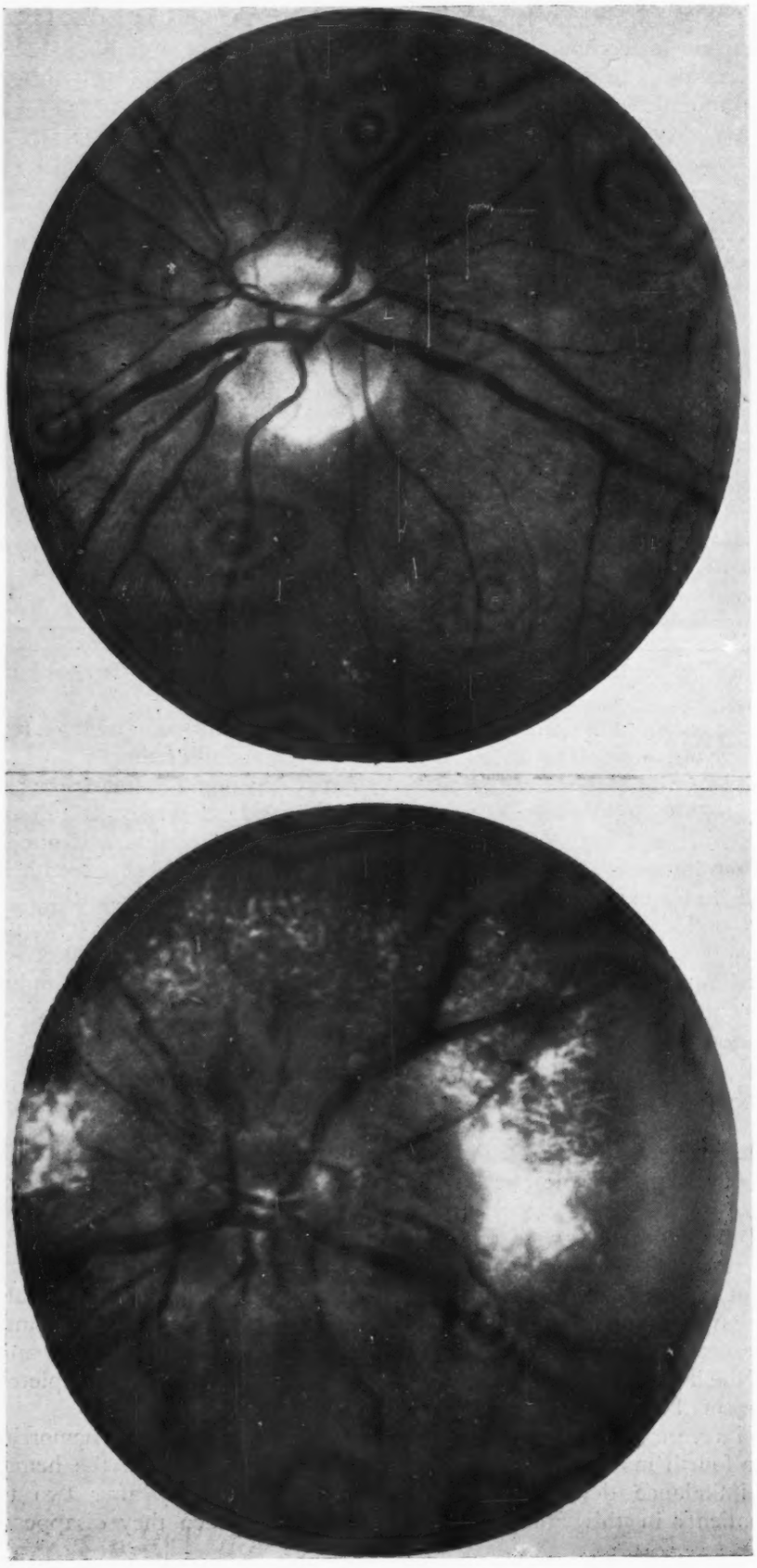
	Disappeared Completely		Disappeared Partially		No Change	
	Number of Patients	Time in Months (averages)	Number of Patients	Time in Months (averages)	Number of Patients	Time in Months (averages)
Papilledema (100 patients)	92	5	3	2	5	4
Hemorrhages (90 patients)	69	8	16	8	5	4
Exudates (94 patients)	56	15	30	7	8	5

* Eyeground photographs available before and 1 to 121 months after treatment with the rice diet was started.

EFFECT OF RICE DIET ON RETINOPATHY

In 100 of the 126 patients with malignant hypertension in whom treatment with the rice diet was used, eyeground photographs are available before and after 1 to 121 months of treatment. (Table VI, Figure 3.) All the 100 patients had papilledema before treatment and in ninety-two it disappeared completely with treatment. The eight in whom papilledema was not affected or did not completely disappear died.

Ninety patients had hemorrhages before treatment. In sixty-nine the hemorrhages disappeared completely after two to thirty-one months. In sixteen they disappeared partially



July, 1954

June, 1944

FIG. 3. Ten year follow-up in malignant hypertension (A. A. H., man, age 47 to 57).

after two to thirty-one months. In five there was no change after two to eight months. In two patients hemorrhages developed during treatment but were not present at the most recent examination. In three patients in whom hemorrhages had disappeared, they recurred and were present at the most recent examination.

2 to 6 mg. (two patients), apresoline® 50 to 150 mg. (twelve patients; one patient has taken as much as 400 mg. of apresoline at times), hexamethonium chloride 250 to 1500 mg. (eleven patients), and raudixin 50 to 150 mg. (nine patients).

Table VII shows the length of treatment with

TABLE VII

FIFTEEN PATIENTS GIVEN HYPOTENSIVE DRUGS

Initials	Fundi before Diet P H E†	Length of Dietary Treatment before Drugs Were Started (mo.)	Chloride Excretion before Drugs (as NaCl mg. per 100 cc. of urine)*	Fundi before Drugs Added P H E†	Medication at Most Recent Examination (mg. daily)			Fundi at Most Recent Examination P H E†
					C_6	Apresoline	Raudixin	
E. N.	+++	30	30	0 0 0		none‖		0 0 0
J. N.	+0+	30	40	0 0 0	1000	100		0 0 0
H. G.	+++	24	28	0 0 0			100	0 0 0
H. L.	+++	21	37	0 0 0		100		0 0 0
L. M.	+++	20	21	0++			100	0+0
J. M.	+++	18	105	0++		75	100‡	0 0 0
W. L.	+++	17	63	0 0 0		none‖		0 0 +
W. R.	+++	14	36	0 0 +		none‖		0 0 +
B. T.	+++	14	23	0 0 0			150	0 0 0
L. R.	+++	9	36	0++		200–400		0 0 0
P. C.	+++	9	26	0++	750	75		0++
J. C.	+++	8	40	0++	750	100	150	0 0 0
J. W.	+0+	6	34	0++	750		150	0 0 0
J. K.	+++	½		+++		none‖		0 0 +
M. B.§	+++	0		+++		100	150	0 0 0

* Should be 5 to 15 mg. per 100 cc. of urine on the basic rice diet and 15 to 25 mg. on the correctly followed "modified" diet.

† PHE stands for papilledema, hemorrhages, exudates.

‡ 3 mg. veraloid plus medication as listed.

§ Had received 25 mg. veraloid before she came to us, dose cut to 6 mg. during first four months, then all drugs stopped and resumed twenty-eight months later. (Chloride excretion 33 mg. per 100 cc. of urine before drugs restarted.)

‖ Had received 50–100 mg. apresoline, 500–1000 mg. hexamethonium, or 100 mg. raudixin singly or in combination for two to ten months, but were not receiving medication at most recent examination.

Ninety-four patients had exudates before treatment. In fifty-six the exudates disappeared completely after two to thirty-four months. In thirty they disappeared partially after one to twenty-two months; in eight there was no change after one to eleven months. In five patients in whom the exudates had disappeared, they were again present at the most recent examination.

After zero to thirty-six, average fifteen, months of treatment by diet alone, fifteen of the one hundred patients were given hypotensive drugs in addition to the strict or modified rice diet for three to thirty, average fourteen, months. The drugs were used singly or in combination. The doses per day were: veraloid

the rice diet before drugs were added, the funduscopic findings before treatment with the rice diet, before the drugs were given and at the most recent examination, and the present medication.

These drugs in the doses in which we have used them have caused a further lowering of the blood pressure in some instances but did not alter the course of the retinopathy nor was there any improvement of hypertensive heart or kidney disease noted which could be attributed to them. Treatment with the drugs was started in only two instances before the disappearance of papilledema and these fifteen patients, therefore, have been included with the other patients.

EFFECTS OF RICE DIET ON PATIENTS FOLLOWED FOR AT LEAST ONE YEAR

There are sixty-one patients who were re-examined here at least one year after treatment with the rice diet had been started. These sixty-one patients include fifty-seven of the sixty-one patients listed as treated for over one year in Table v, three patients who are listed as treated for less than one year but who were re-examined here one year after treatment with the rice diet had been started, and one patient who was followed here for thirteen months but whose present condition is not known. Of the sixty-one patients eighteen had a total PSP excretion of 16 to 35 per cent in two hours; twenty-three had a total PSP excretion of 36 to 55 per cent in two hours; 20 had a total PSP excretion of 56 to 88 per cent in two hours. The effects of the rice diet on blood pressure, serum cholesterol, blood non-protein nitrogen, T_1 in the electrocardiogram, cardiothoracic ratio and renal function are shown in Tables VIII to XIV. A comparison is made of the findings during the period of "strictest adherence to the rice diet" with those at the most recent examination.

Table VIII
BLOOD PRESSURE IN SIXTY-ONE PATIENTS TREATED WITH RICE DIET*

Before Treatment (average)	During Period of Strictest Adherence to Rice Diet (average†)	At Most Recent Examination (average‡)
219/134	168/105	184/109

* Followed for at least one year.
† After 2 to 13, average 4, months.
‡ After 1 to 9½, average 4, years.

Even during the period of "strictest adherence to the rice diet" determinations of the chloride excretion in the urine showed that some patients were deviating from the prescribed diet; the chloride excretion of these sixty-one patients during the period of "strictest adherence to the rice diet" was 5 to 52, average 18, mg. per 100 cc, expressed as sodium chloride.

Table VIII lists the average blood pressures before treatment, during the period of "strictest adherence to the rice diet," and at the most recent examination. The average blood pressure of these sixty-one patients decreased from 219/134 to 168/105 during the period of "strictest adherence to the rice diet." In eighteen (30 per cent) of the sixty-one patients the blood pressure decreased to 149/99 or below; in eight (13 per cent) of the sixty-one to 125/89 or below during the period of "strictest adherence to the rice diet."

Table IX
BLOOD NPN IN FORTY PATIENTS TREATED WITH RICE DIET*

Range before Treatment (NPN mg. per 100 cc. of blood)	Number of Patients	Before Treatment (averages)	During Period of Strictest Adherence to Rice Diet (averages†)	At Most Recent Examination (averages‡)
36–45	22	39	33	32
46–75	18	53	36	45

* Followed for at least one year. Initial NPN 36 mg. or more per 100 cc. of blood.
† After 2 to 9, average 4, months.
‡ After 1 to 9½, average 3, years.

Thirty-two of the sixty-one patients were following the rice diet well or moderately well at the most recent examination (chloride excretion, as NaCl, 24 mg. per 100 cc. of urine, average of the most recent determinations, one to eight and one-half, average five, years after the rice diet had been started). The average blood pressure of these thirty-two patients at the most recent examination was 175/105 as compared to 217/132 before treatment and 165/104 after the first two to six, average four, months on the rice diet.

The other twenty-nine patients followed the diet moderately well to poorly most of the time since the initial period of strict treatment here (chloride excretion, as NaCl, 65 mg. per 100 cc. of urine, average of most recent determinations, 1 to nine and one-half, average three, years after the rice diet was started). The average blood pressure of these twenty-nine patients at the most recent examination was 193/114 as compared to 220/136 before treatment and 170/106 after the first two to thirteen, average five, months on the rice diet.

In fifty-nine of the sixty-one patients blood NPN determinations are available before treatment, during the period of "strictest adherence to the rice diet," and at least one year after treatment was started. The NPN was elevated in forty of these patients and Table IX shows the changes during treatment. In thirty-three (82 per cent) it was lower at the most recent examination than it had been initially. Three patients, who had had a normal NPN before

the rice diet was started, developed azotemia. All three had followed the diet poorly, chloride excretion 92 mg. per 100 cc. of urine, average of four to seven determinations each; the NPN, average, was 32 mg. per 100 cc. of blood before treatment, 31 mg. after the first four months, average, on the rice diet and 51 mg., two to five, average three, years after treatment with the rice diet had been started.

TABLE X

SERUM CHOLESTEROL IN FORTY-SIX PATIENTS TREATED WITH RICE DIET*

Serum Cholesterol Level	Number of Patients	Serum Cholesterol (mg./100 cc.)		
		Before Treatment (averages)	During Period of Strictest Adherence to Rice Diet (averages†)	At Most Recent Examination (averages‡)
Increased	6	259	233	330
Decreased:	40	288	199	200
to 219 or below	32	282	192	183
to 220 or above	8	312	230	266

* Followed for at least one year. Initial cholesterol concentration in serum 220 mg. per 100 cc. or above.
† After 2 to 9, average 4, months.
‡ After 1 to 7, average 3, years.

In fifty-five of the sixty-one patients the cholesterol concentration in the serum was determined before treatment, during the period of "strictest adherence to the rice diet" and one to seven years after the treatment had been started.

Forty-six (84 per cent) of these fifty-five patients had a serum cholesterol concentration of 220 mg. per cent or more when first seen here, and the data on these patients are shown in Table x. Only two of these forty-six patients had an increase in the serum cholesterol concentration during treatment with the strict rice diet; the average cholesterol concentration in these two patients was 257 mg. per 100 cc. of serum before treatment and 290 mg. after the first four months, average, on the rice diet.

In six patients (13 per cent) the serum cholesterol was higher at the most recent examination three to six, average four, years after treatment with the rice diet was started than before. In forty (87 per cent) of the forty-six patients with an initial cholesterol concentration in the serum above 220 mg. the cholesterol concentration in the serum decreased; in thirty-two (70 per cent) of the forty-six it decreased to 219 mg. per 100 cc. or below. In two of the nine patients who had had a cholesterol concentration in the serum of 219 mg. or below per 100 cc. before treatment, the cholesterol concentration in the serum increased to 220 mg. or above. In these two patients the cholesterol concentration in the serum, average, was 215 mg. per 100 cc. before treatment, 212 mg. after the first three months, average, on the rice diet and 252 mg. two and one-half years, average, after treatment had been started.

TABLE XI

T_1 IN THE ELECTROCARDIOGRAM IN FORTY-NINE PATIENTS TREATED WITH RICE DIET*

	Before Treatment (Number of Patients)	During Period of Strictest Adherence to Rice Diet (Number of Patients)	At Most Recent Examination (Number of Patients)
T_1 upright	14	38	28
T_1 diphasic	10	4	5
T_1 inverted	25	7	15†

* Followed for at least one year.
† One patient who was following the diet poorly developed a left bundle branch block.

In forty-nine of the sixty-one patients electrocardiograms are available for comparison (no digitalis, no infarction, etc.) before treatment, during the period of "strictest adherence to the rice diet" and one to nine and one-half years after treatment had been started. (Table XI.) In thirty-five (71 per cent) T_1 was abnormal before treatment; in ten it was diphasic; in twenty-five it was inverted.

In fourteen patients T_1 was upright before the rice diet was started; in none of the fourteen was there a change in the direction from upright to inverted after one and one-half to eight and one-half, average four, years. In nine of the ten patients in whom T_1 was diphasic before treatment it became normally upright after three to thirty-two, average eight, months of adequately followed dietary treatment. In one patient, it remained diphasic. In seven of the twenty-five patients in whom T_1 was inverted before treatment it remained inverted after one to three, average two, years. In eighteen (72 per cent) of the twenty-five patients there was a change in the direction from inverted to upright; in three T_1 became diphasic after seven to ten, average eight, months; in fifteen it

became normally upright after three to seventeen, average eight, months.

In twelve of the twenty-seven in whom the electrocardiogram had initially shown improvement it again became more abnormal. Nine of the twelve were following the diet poorly. In one of the nine patients a left bundle branch block developed.

In forty-nine of the sixty-one patients comparable chest films (no digitalis) are available before treatment, during the period of "strictest adherence to the rice diet" and at the most recent examination one to nine and one-half, average three, years after treatment had been started. (Table XII.) Before treatment the cardiothoracic ratio was 0.42 or below in only three patients (6 per cent); during the period of "strictest adherence to the rice diet" it was 0.42 or below in twenty-four (49 per cent). The cardiothoracic ratio before treatment was over 0.48 in twenty-nine (59 per cent); in nineteen it was 0.48 to 0.52 and in ten it was 0.53 to 0.59. During the period of "strictest adherence to the rice diet," the cardiothoracic ratio was over 0.48 in only seven (14 per cent). In these seven patients the average cardiothoracic ratio had decreased from 0.54 to 0.49 after the first five months, average, on the rice diet.

In thirty-six (73 per cent) of the forty-nine patients the decrease in cardiothoracic ratio during the period of "strictest adherence to the rice diet" was more than 10 per cent. In twenty-one of these thirty-six patients the cardiothoracic ratio at the most recent examination had again increased by 10 per cent or more. Fourteen of the twenty-one patients in whom cardiomegaly recurred were following the diet poorly; the cardiothoracic ratio, average, in these fourteen patients increased from 0.43 after the first four months, average, on the rice diet to 0.50 at the most recent examination. In the seven patients who were following the diet "satisfactorily" and in whom cardiomegaly recurred, the cardiothoracic ratio increased from average figures of 0.40 to 0.46.

TABLE XII

CARDIOTHORACIC RATIO IN FORTY-NINE PATIENTS TREATED WITH RICE DIET*

Initial Cardiothoracic Ratio (range)	Before Treatment		During Period of Strictest Adherence to Rice Diet		At Most Recent Examination	
	Number of Patients	CT Ratio (averages)	Number of Patients	CT Ratio (averages†)	Number of Patients	CT Ratio (averages‡)
0.36 to 0.42	3	0.41	24	0.40	12	0.41
0.43 to 0.47	17	0.45	18	0.45	16	0.46
0.48 to 0.52	19	0.50	6	0.49	16	0.50
0.53 to 0.59	10	0.56	1	0.53	5	0.55
0.36 to 0.59	49	0.49	49	0.43	49	0.46

* Followed for at least one year.
† After 1 to 22, average 6, months.
‡ After 1 to 9½, average 3, years.

TABLE XIII

KIDNEY FUNCTION (PSP EXCRETION) IN FORTY PATIENTS TREATED WITH RICE DIET*

	Number of Patients	Total PSP Excretion in 2 Hours (%)		Length of Time in Months (averages)
		Before Treatment (averages)	At Most Recent Examination (averages)	
Diet poorly followed (after initial period):	14	49	43	48
Increased or unchanged	5	52	59	45
Decreased	9	47	35	50
Diet well followed:	26	44	47	46
Increased or unchanged	17	43	54	51
Decreased	9	44	37	38

* Followed for at least two years.

Table XIII shows the change in total PSP excretion in two hours in forty patients treated with the rice diet, strict and modified, for two years or longer. In nine (64 per cent) of

the fourteen who followed the diet poorly after the initial period of treatment, the PSP excretion decreased; in five (36 per cent) it increased. In nine (35 per cent) of the twenty-six who followed the diet well it decreased; in seventeen (65 per cent) it increased.

TABLE XIV
KIDNEY FUNCTION (PSP EXCRETION) IN TWELVE PATIENTS TREATED WITH RICE DIET*

	Number of Patients	Total PSP Excretion in 2 Hours (%)	
		Before Treatment (averages)	At Most Recent Examination (averages)
Diet poorly followed (after initial period)	5	53	44
Followed diet well	7	52	60

* Followed for at least five years.

There are twelve patients in whom repeated determinations of the total PSP excretion in two hours are available after five years or more of observation. (Table XIV.) Five followed the diet poorly; the average PSP excretion in two hours of these five patients decreased from 53 to 44 per cent. Seven have adhered to the diet well; in these seven the average PSP excretion in two hours has increased from 52 to 60 per cent.

It usually takes at least three to four months of intensive dietary treatment to produce a significant decrease in the heart size and blood pressure and it frequently takes over one year for the inverted T_1 in the electrocardiogram to become normally upright. For improvement in kidney function at least two to three years are needed.

COMMENT

When treatment with the rice diet was started in 1939 it was thought that extreme dietary restriction would have to be continued indefinitely to compensate for an underlying renal metabolic dysfunction. At present we have quite a few patients who have been able to resume a salt-poor, fat-poor diet and some who, after an adequate period of intensive treatment first with a strict and then with a modified rice diet, have been able to tolerate a general diet without recurrence of vascular disease.

In patients with malignant hypertension treated with the rice diet before the PSP excretion in two hours has decreased to less than 35 per cent, the prognosis is no longer as unfavorable as it was. Sixty (84 per cent) of the seventy-one patients with a total PSP excretion of 36 per cent or more in two hours survived one year (Table II) and had overcome the malignant phase of the hypertensive vascular disease. Of these sixty patients, thirty (Fig. 2) continued to follow the rice diet; twenty-eight (93 per cent) of the thirty are still living four years after initiation of treatment. However, since most cases of malignant hypertension are preceded by known "benign" hypertensive vascular disease, malignant hypertension can now be regarded as a preventable condition. Hypertensive vascular disease, no matter how mild the symptoms, should be treated immediately and vigorously as soon as the diagnosis has been established, and in those patients who have already developed the malignant phase and have been successfully treated intensive dietary treatment should not be discontinued before the underlying disease has disappeared.

SUMMARY

One hundred seventy-seven patients with hypertensive vascular disease with papilledema (confirmed by eyeground photographs) were seen between October, 1942, and October, 1953. In six patients follow-up information is inadequate or the treatment period too short for evaluation.

In thirty-three patients with hypertensive neuroretinopathy who were willing to be treated with the rice diet, electrolyte imbalance developed within the first three months on the rice diet. Treatment with drastic salt restriction therefore could not be carried out, but additional NaCl or other chloride was given. In thirty-one of these thirty-three patients the total PSP excretion in two hours was below 36 per cent. All thirty-three patients died.

In eighteen patients treatment with the rice diet was not carried out at any time; only one of these is still living.

In 120 patients with hypertensive neuroretinopathy treatment with the rice diet was carried out. The period of treatment was from 1 to 117 months. In 83 of the 120 patients the

total PSP excretion in two hours was below 55 per cent. (This includes four patients in the terminal stage of the disease, in whom the PSP was not measured.) Forty-seven (57 per cent) of these patients survived one year; twenty-six (31 per cent) are still living four and one-fourth years (average) after treatment was started. In thirty-seven patients the total PSP excretion was 56 per cent or more in two hours; thirty-four (92 per cent) survived one year; twenty-six (70 per cent) are still living five years (average) after treatment was started.

One hundred of the 120 patients were followed after the initial period of the treatment with the rice diet, and in these patients the relation of the length of time of supervised treatment to the survival time could be studied. In 39 of the 100 patients the period of supervised treatment was two to twelve months. Seven of the thirty-nine died during this period while presumably still following the diet; only three of the seven were following it correctly. Thirty-two of the thirty-nine were treated for two to twelve months, and then to a greater or lesser extent discontinued the treatment; only six (19 per cent) of the thirty-two are still living.

Eighteen of the 100 patients were treated one to seven and one-half, average three, years and then to a greater or lesser extent discontinued the treatment. Nine of these (50 per cent) are still living.

Forty-three of the 100 patients were treated over one year with the rice diet and continued treatment. Thirty-seven (86 per cent) of these are still living; of the six who died, only three were following the diet correctly.

The effect of the rice diet on retinopathy was studied in 100 patients in whom eyeground photographs were available. In ninety-two of the 100 patients, papilledema disappeared completely.

The effects of the rice diet on blood pressure, serum cholesterol, blood non-protein nitrogen, T_1 in the electrocardiogram, cardiothoracic ratio and renal function were studied in sixty-one patients who were re-examined here at least one year after treatment had been started. A comparison of the findings before treatment, during the period of "strictest adherence to the rice diet" and at the most recent examination shows that the "strictest adherence to the rice diet" produces the most favorable results. Dietary modifications therefore should be made gradually and with careful observations of blood pressure readings, blood chemical findings, electrocardiograms, chest films, eyeground photographs, etc.

The results are interpreted as indicating that intensive dietary treatment should be started as early as possible and continued until all signs of the vascular disease have disappeared.

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Effects of Restriction of Dietary Fat and Cholesterol upon Serum Lipids and Lipoproteins in Patients with Hypertension*

FREDERICK T. HATCH, M.D.,† LIESE L. ABELL, PH.D.
and FORREST E. KENDALL, PH.D.
New York, New York

THE effects of drastic restriction of dietary fat intake and elimination of cholesterol intake upon serum lipid patterns in patients with hypertension have been presented previously as part of an investigation of the Kempner rice diet.[1] This therapeutic diet, which contains no cholesterol, practically no fat and only minimal amounts of protein, is of particular interest in the study of lipid metabolism in man. The investigations previously reported gave rise to the following findings: (1) A moderate decline in the average serum cholesterol levels was seen in most patients on the rice diet; in no case did the levels decrease below the normal range. (2) A neutral fat lipemia, together with an increase in serum lipid phosphorus and a decreased percentage of esterified cholesterol, was observed in one-third of the patients. The decreased percentage of esterified cholesterol was associated with the development in some patients of marked sensitivity to dicumarol and of increased values for bromsulfthalein retention and thymol turbidity. This pointed to the possibility that the effects on the serum lipids were brought about through impairment of hepatic function.

The present report extends the studies to a larger number of patients and in addition presents observations during lesser degrees of restriction of dietary fat and cholesterol. Data on serum lipoprotein concentrations, as determined with the ultracentrifuge, are presented.

Several workers have correlated the serum cholesterol concentration in man with the dietary intake of cholesterol.[2–5] Within a broad range of intake levels there was no correlation with the serum total cholesterol. However, the report by Starke of studies in Kempner's clinic demonstrated that drastic restriction of both fat and cholesterol in the rice diet produced significant decreases in the free and esterified cholesterol of serum.[6]

Experimental studies in man by Keys,[7] by Hildreth[8] and by Mayer[9] and their co-workers indicated that the intake of fats, both animal and vegetable in origin, has a definite influence upon the serum cholesterol level. On the other hand Kinsell and co-workers asserted that fats of vegetable origin do not tend to maintain high serum cholesterol levels and may even have a depressant effect.[10] The weight reduction studies of Walker et al. showed that in the presence of low to moderate fat in the diet, the serum cholesterol and lipoproteins may vary in proportion to the total caloric intake.[11]

Investigations of the effects of dietary variations upon the serum neutral fat or total lipids have not been reported, except in the previous communication from this laboratory.[1] Thus the lipemia observed in certain subjects during rice diet treatment has not received further elucidation.

MATERIAL AND METHODS

The patient material for this investigation consisted of a group of hospitalized individuals with severe essential hypertension. Most of the subjects had initial resting blood pressures greater than 200/120 mm. Hg and gave evidence of impaired function of the eyes, brain,

* From the Research Service, First (Columbia University) Division, Goldwater Memorial Hospital, Department of Hospitals, New York City and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York. Aided by grants from the National Heart Institute, The Public Health Research Institute of the City of New York, Inc., The Josiah Macy Foundation and the Albert and Mary Lasker Foundation.

† Present address: U.S. Army, Medical Nutrition Laboratory, Fitzsimons Army Hospital, Denver, Colo.

heart or kidneys. Patients with detectable diabetes mellitus and glomerulonephritis were excluded. The program had the following dietary phases:

Phase 1: A control period of four to eighteen weeks was conducted on a salt-poor diet of normal fat content (Diet I) served from the hospital diet kitchen.

Phase 2: The period on the control diet was followed by a period ranging from four to twenty weeks on the unmodified Kempner rice diet (Diet IV). Forty-four patients have been studied in both Phases 1 and 2.

Phase 3: Smaller groups of patients were studied on diets providing levels of fat and cholesterol intake intermediate between those of Phases 1 and 2. (*a*) Ten of the forty-four patients of Phase 2 were subsequently studied on the rice diet supplemented by various amounts of protein and fat in the form of low-sodium milk and a protein-carbohydrate powder* (Diet III). (*b*) Ten of the forty-four patients of Phase 2 subsequently received a special low-sodium diet of greater palatability than the rice diet (Diet II). (*c*) Six additional patients were studied on the special low-sodium diet (Diet II) without a preliminary period on the rice regimen. The higher fat and protein contents of this diet were provided by lonalac,® protinal® and meat.

All diets except the hospital salt-poor diet used in Phase 1 were served under strict control from a special diet kitchen.[1] The composition of the diets is described in Table I. Levels of daily fat intake of 85 gm., 55 gm., 20 to 40 gm. and 3 gm. were provided by the different regimens. Daily cholesterol intakes corresponding to the fat intake levels were approximately 1.0, 0.10, 0.03 to 0.25 and 0 gm. per day. Each of the restrictive diets (II, III, IV) was supplemented by one multiple vitamin capsule† and 0.2 gm. of ferrous sulfate daily.

Serum was analysed for free and total cholesterol, lipid phosphorus and neutral fat at weekly or bi-weekly intervals throughout the study. During the first year of the program all bloods for analysis were drawn before the patient had breakfast. It was found that on the diets under study there was no significant difference in any of the serum lipid levels between samples taken during the fasting state and after the morning meal. Therefore during the last two years the samples were taken within two hours after the patient had breakfast.

TABLE I
COMPOSITION OF DIETS

Diet	Control (Diet I)	Special Low-Sodium (Diet II)	Modified Rice (Diet III)	Rice (Diet IV)
No. of patients studied	44	16	10	44
Calories per day	2220	2140	2600	2390
Sodium chloride (gm./day)	2.5	0.25	0.25	0.25
Protein (gm./day)	85	90	40–80	30
Carbohydrate (gm./day)	280	320	530	560
Fat (gm./day)	85	55	20–40	3
Cholesterol (gm./day)	1.0	0.10*	0.03–0.25*	0

* In the early part of this study the fat content of lonalac was derived entirely from milk. Five patients on Diet III received this product which provided about 0.25 gm. of cholesterol per day. More recently only one-fifth of the fat content of lonalac has been derived from milk and the remainder from coconut oil. Five patients on Diet III and all of those on Diet II received the latter product which provided 30 to 40 mg. of cholesterol daily. An additional small amount of cholesterol in Diet II was derived from the meat.

Samples for the ultracentrifugal determination of the S_f 12–20 and S_f 20–100 lipoprotein fractions were obtained after the patients had been on the specified diet for two to eighteen weeks. These samples were refrigerated and shipped by air express to Dr. J. W. Gofman who performed the analyses according to his published technic.[12,13] Only fasting bloods were used for ultracentrifugal lipoprotein analyses.

Free and total serum cholesterol were determined by the method of Schoenheimer and Sperry.[14,15] Lipid phosphorus was determined by the method of Fiske and Subbarrow[16] after extraction and wet ashing of the lipids. Conversion of lipid phosphorus to phospholipids was made using the multiplication factor of twenty-five. Total lipid was measured gravimetrically on the petroleum ether-soluble portion of an alcohol-ether extract of serum made according to the method of Bloor.[17]

It was found that the gravimetric method for total lipid suffered from errors of considerable magnitude. The weighed residue contained

* Lonalac is a low-sodium milk powder having the same protein and fat content as whole milk when diluted as directed by the manufacturer. Generous supplies were provided by the Mead Johnson & Co., Evansville, Ind. Protinal (National Drug Co.) was blended with lonalac in some instances to enrich the protein content.

† Vi-penta Perles Forte® were kindly provided by Hoffmann-La Roche, Inc., Nutley, N. J.

both inorganic salts and water. The gravimetric method was therefore compared with the manometric lipid carbon procedure of Van Slyke and Folch.[18] This comparison demonstrated that subtraction of a constant value of 200 mg. per cent from the observed total lipid levels obtained by the gravimetric method gave agreement within plus or minus 5.5 per cent on the average with the Van Slyke-Folch method. This correction has been applied to all total lipid values.

The concentration of the serum neutral fat was estimated by subtracting from the weight of total lipids the sum of the amounts of phospholipids, total cholesterol and the fatty acids of the cholesterol ester fraction (0.7 × weight of cholesterol in the esters).

Since calculation of the neutral fat content incorporates the technical errors of four different analytic procedures, no great weight can be given to the absolute values reported. However, the changes observed on the different diets are much larger than can be attributed to experimental errors.

The full effects of each new dietary regimen on the serum lipids were generally established within one week after institution of the change. Therefore the serum lipid levels reported are the averages of values observed after the first week on a given diet. The composition of the preceding diet had no significant residual influence on the lipid levels after that time.

TABLE II

SUMMARY OF CHANGES IN SERUM LIPID LEVELS DURING RESTRICTION OF DIETARY FAT AND CHOLESTEROL

Diets	No. of Patients	Intake (gm./day)		Total Cholesterol (mg. %)	Free Cholesterol (mg. %)	Lipid Phosphorus (mg. %)	Neutral Fat (mg. %)
		Fat	Cholesterol				
Control.....	16	85	1.0	219 ± 11*	64 ± 5	9.7 ± 0.5	230 ± 30
Diet II.....	16	55	0.1	207 ± 8	64 ± 5	9.6 ± 0.3	280 ± 20
Difference...	..	.....	....	−12 ± 14†	0 ± 7	−0.1 ± 0.6	+50 ± 36
Control.....	10	85	1.0	217 ± 12	61 ± 4	9.8 ± 0.5	190 ± 20
Diet III.....	10	20–40	0.03	191 ± 12	59 ± 2	10.1 ± 0.6	370 ± 50
Difference...	..	.....	....	−26 ± 17	−2 ± 4	+0.3 ± 0.8	+180‡ ± 54
Control.....	44	85	1.0	224 ± 6	64 ± 2	10.0 ± 0.3	220 ± 20
Diet IV.....	44	3	0.0	191 ± 6	61 ± 1	10.0 ± 0.4	370 ± 35
Difference...	..	.....	....	−33‡ ± 9	−3 ± 2	0.0 ± 0.5	+150‡ ± 40

Key to diets: I, control diet; II, special low sodium diet; III, modified rice diet; IV, rice diet.

* Standard error of the mean: $\sigma_{\bar{x}} = \frac{\sigma}{\sqrt{N}}$.

† Standard error of the difference: $\sigma_D = \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$.

‡ Significant difference between control and experimental values.

RESULTS

Serum Lipid Levels on Control Period Diet. During the control period (Diet I) the hypertensive patients exhibited serum lipid levels which differed little from those of a series of healthy ambulatory subjects.* The two series were fairly matched for age and sex distribution except that there was a lower proportion of females above the age of fifty years in the healthy group than in the hypertensive series. Average serum lipid levels in fifty-one patients with hypertension were compared with single determinations of the lipid pattern in thirty-nine subjects who were leading normal lives and in

* We are indebted to Dr. Alfred Steiner for serum lipid data on the healthy subjects. These individuals showed no abnormal findings upon physical examination or in the blood count, sedimentation rate, urinalysis, electrocardiogram and chest x-ray.

TABLE III

AVERAGE SERUM LIPID LEVELS DURING PERIODS OF CONTROLLED FAT AND CHOLESTEROL INTAKE

Patient	Age and Sex	Diet	Intake (gm./day)		Total Cholesterol (mg. %)	Free Cholesterol (mg. %)	Lipid Phosphorus (mg. %)	Neutral Fat (mg. %)
			Fat	Cholesterol				
A. A.	65, M	I	85	1.0	220	58	9.4	230
		IV	3	0.0	210	76	12.8	700
A. B.	35, F	I	85	1.0	200	49	7.8	150
		IV	3	0.0	160	45	8.6	170
F. B.	58, M	I	85	1.0	200	62	11.5	270
		IV	3	0.0	250	93	15.9	1080
T. B.	56, F	I	85	1.0	240	90	14.9	490
		IV	3	0.0	300	100	14.4	550
H. C.	63, M	I	85	1.0	210	60	8.6	280
		IV	3	0.0	160	52	8.1	510
I. C.	56, F	I	85	1.0	250	68	11.3	370
		IV	3	0.0	220	73	11.0	530
J. Co.	32, F	I	85	1.0	160	46	7.8	100
		IV	3	0.0	140	39	7.3	240
R. C.	48, M	I	85	1.0	230	62	10.9	230
		IV	3	0.0	150	47	8.5	240
S. D.	52, M	I	85	1.0	190	52	8.6	120
		IV	3	0.0	170	47	8.1	200
R. E.	40, F	I	85	1.0	190	57	8.4	90
		IV	3	0.0	130	40	7.2	150
P. F.	21, F	I	85	1.0	190	52	9.3	280
		IV	3	0.0	130	44	8.3	390
A. H.	54, M	I	85	1.0	200	57	9.2	270
		IV	3	0.0	220	65	11.5	520
W. H.	60, M	I	85	1.0	260	72	10.8	....
		IV	3	0.0	200	53	8.5	....
J. I.	41, F	I	85	1.0	220	62	10.3	320
		IV	3	0.0	190	63	10.2	220
D. K.	48, F	I	85	1.0	220	61	9.8	120
		IV	3	0.0	170	47	8.1	180
E. K.	50, F	I	85	1.0	200	...	9.3	270
		IV	3	0.0	160	...	8.6	370
G. K.	48, M	I	85	1.0	240	72	10.8	360
		IV	3	0.0	190	57	9.5	290
C. L.	54, M	I	85	1.0	320	87	13.3	470
		IV	3	0.0	250	84	13.7	580
S. L.	60, M	I	85	1.0	280	80	11.2	100
		IV	3	0.0	210	61	9.3	130
A. Ma.	44, F	I	85	1.0	290	79	13.9	....
		IV	3	0.0	260	75	12.9	....
A. Mo.	42, F	I	85	1.0	240	71	10.3	110
		IV	3	0.0	170	54	9.4	260

TABLE III (*Continued*)

Patient	Age and Sex	Diet	Intake (gm./day)		Total Cholesterol (mg. %)	Free Cholesterol (mg. %)	Lipid Phosphorus (mg. %)	Neutral Fat (mg. %)
			Fat	Cholesterol				
B. M.	55, M	I	85	1.0	220	60	9.3	310
		IV	3	0.0	210	69	11.7	720
T. M.	46, M	I	85	1.0	280	84	12.7	340
		IV	3	0.0	200	60	9.6	190
M. P.	57, M	I	85	1.0	250	75	9.6	40
		IV	3	0.0	190	68	11.8	740
P. R.	61, M	I	85	1.0	170	49	8.2	140
		IV	3	0.0	130	43	7.4	170
Y. R.	44, F	I	85	1.0	290	86	12.7	320
		IV	3	0.0	250	77	12.7	250
M. Su.	67, F	I	85	1.0	220	64	10.1	170
		IV	3	0.0	240	94	13.4	720
J. W.	54, M	I	85	1.0	240	78	9.1	200
		IV	3	0.0	190	63	8.8	230
L. B.	49, M	I	85	1.0	200	52	8.2	240
		II	55	0.1	160	48	8.6	380
M. F.	40, M	I	85	1.0	200	65	8.0	330
		II	55	0.1	190	54	9.6	320
E. L.	62, F	I	85	1.0	230	70	12.4	420
		II	55	0.1	240	76	11.6	290
G. S.	47, M	I	85	1.0	330	99	15.2	530
		II	55	0.1	280	88	12.7	510
B. V.	54, F	I	85	1.0	270	71	11.2	160
		II	55	0.1	240	75	11.2	280
M. W.	55, F	I	85	1.0	250	73	11.1	250
		II	55	0.1	250	79	10.9	350
F. S.	66, M	I	85	1.0	190	52	8.0	180
		III	20–40	0.25	140	44	7.5	210
D. G.	50, M	I	85	1.0	220	66	9.4	190
		II	55	0.1	220	70	10.1	290
		IV	3	0.0	190	58	9.0	220
B. F.	51, F	I	85	1.0	210	61	8.9	170
		II	55	0.1	190	62	9.1	220
		IV	3	0.0	200	70	10.3	370
J. K.	49, M	I	85	1.0	200	58	8.7	90
		II	55	0.1	180	61	8.9	240
		IV	3	0.0	150	48	8.1	210
J. R.	48, M	I	85	1.0	240	68	9.7	190
		II	55	0.1	220	67	9.6	240
		IV	3	0.0	210	76	9.6	320
L. S.	56, M	I	85	1.0	180	61	7.8	190
		II	55	0.1	160	46	7.1	190
		IV	3	0.0	160	53	6.8	200

TABLE III (*Continued*)

Patient	Age and Sex	Diet	Intake (gm./day)		Total Cholesterol (mg. %)	Free Cholesterol (mg. %)	Lipid Phosphorus (mg. %)	Neutral Fat (mg. %)
			Fat	Cholesterol				
M. Si.	37, M	I	85	1.0	150	35	7.3	130
		II	55	0.1	210	67	9.0	260
		IV	3	0.0	160	48	7.8	110
D. W.	46, F	I	85	1.0	230	71	10.0	250
		II	55	0.1	220	66	9.3	260
		IV	3	0.0	190	63	10.2	480
J. Ce.	46, F	I	85	1.0	240	61	10.4	160
		III	20–40	0.04	270	75	12.4	220
		IV	3	0.0	230	66	11.3	360
R. G.	53, M	I	85	1.0	290	88	12.5	280
		III	20–40	0.25	150	41	7.7	170
		IV	3	0.0	190	56	9.8	240
M. K.	54, F	I	85	1.0	250	73	11.6	260
		III	20–40	0.25	200	68	11.9	700
		IV	3	0.0	180	64	11.4	440
J. N.	46, F	I	85	1.0	240	65	9.7	250
		III	20–40	0.25	220	70	12.4	550
		IV	3	0.0	210	66	12.0	580
C. R.	49, M	I	85	1.0	160	53	7.9	140
		III	20–40	0.25	160	53	9.2	330
		IV	3	0.0	150	49	9.2	310
A. W.	65, M	I	85	1.0	180	48	8.5	170
		III	20–40	0.04	200	60	10.1	370
		IV	3	0.0	160	50	8.5	150
V. B.	48, F	I	85	1.0	220	59	9.6	50
		II	55	0.1	200	58	9.4	230
		III	20–40	0.04	170	54	8.6	340
		IV	3	0.0	180	56	8.2	110
J. M.	44, M	I	85	1.0	200	58	9.0	160
		II	55	0.1	190	56	9.2	250
		III	20–40	0.04	210	64	11.4	510
		IV	3	0.0	190	72	11.6	640
S. R.	36, F	I	85	1.0	200	56	10.9	280
		II	55	0.1	180	63	8.6	210
		III	20–40	0.04	190	56	10.0	280
		IV	3	0.0	190	55	10.0	330

Key to diets: I, control diet; II, special low sodium diet; III, modified rice diet; IV, rice diet.

whom medical examination revealed no evidence of disease.

No appreciable difference existed between the two groups in average levels of free and esterified cholesterol and lipid phosphorus. The average serum neutral fat level was 46 mg. per cent higher in the patients with hypertension; this difference was statistically significant ($P = 0.05$).

Effects of Restriction of Dietary Fat and Cholesterol on Serum Lipids and Lipoproteins. The average changes in the serum lipid levels observed during restriction of dietary fat and cholesterol are summarized in Table II. The mean lipid concentrations observed upon each of the experimental diets are compared with those of the control period. The only statistically significant changes were a 15 per cent decrease in serum total cholesterol on the rice diet (Diet IV), a 95 per cent increase in serum neutral fat on the rice diet supplemented with from 20 to 40 gm. of fat

per day (Diet III) and a 68 per cent increase in serum neutral fat on the unmodified rice diet (Diet IV).

The average serum lipid levels observed in the individual hypertensive patients during the different dietary periods are given in Table III.

TABLE IV
SUMMARY OF CHANGES IN SERUM LIPOPROTEIN LEVELS DURING RESTRICTION OF DIETARY FAT AND CHOLESTEROL

Diet	No. of Patients	Intake (gm./day)		Serum Lipoproteins (mg. %)	
		Fat	Cholesterol	Sf 12–20	Sf 20–100
Control	9	85	1.0	59	93
Diet II	9	55	0.1	66	106
Difference	..	..	...	+7	+13
Control	18	85	1.0	56	96*
Diet IV	18	3	0.0	65	194*
Difference	..	..	...	+9	+98*

Key to diets: I, control diet; II, special low sodium diet; III, modified rice diet; IV, rice diet
* Data on Sf 20–100 fraction were available in only ten patients.

It will be noted that the shift from the control to the experimental diets was followed by changes which varied greatly among the different subjects.

The changes from control levels in the average serum total cholesterol occurring on the rice diet ranged in different individuals from a decrease of 100 mg. per cent to an increase of 60 mg. per cent. Serum free cholesterol changes ranged from a decrease of 32 mg. per cent to an increase of 31 mg. per cent; lipid phosphorus from a decrease of 3.1 mg. per cent to an increase of 4.4 mg. per cent; and neutral fat from a decrease of 150 mg. per cent to an increase of 810 mg. per cent. In the smaller groups of patients studied on Diets II and III there was also little uniformity of the response in the serum lipids.

The average changes in the serum lipoprotein levels observed during restriction of dietary fat and cholesterol are summarized in Table IV. The mean lipoprotein concentrations observed upon two of the experimental diets (Diets II and IV) are compared with those of the control period. The only statistically significant change was a 100 per cent increase in the concentration of the S_f 20–100 lipoprotein fraction on the rice diet (Diet IV).

The serum lipoprotein concentrations observed in individual subjects during the different dietary periods are recorded in Table V, together with the serum lipid values obtained upon the same serum samples. As in the case of the serum lipids the response of the serum lipoproteins to the experimental diets varied greatly among different subjects.

The serum lipid and lipoprotein levels determined throughout the studies on two representative patients are illustrated in Figures 1 and 2.

Fluctuation of Serum Lipid Components. Many of the hypertensive patients showed large fluctuations of the serum lipid concentrations in the course of serial determinations. These fluctuations were not appreciably affected by restrictions of dietary fat and cholesterol. Forty-eight patients were observed for average periods of six weeks on the control diet and eight weeks on the rice diet. The average ranges of fluctuation (difference between lowest and highest values in individual patients) were as follows: total cholesterol control diet 47 mg. per cent, rice diet 46 mg. per cent; lipid phosphorus control diet 1.6 mg. per cent, rice diet 2.4 mg. per cent; neutral fat control diet 190 mg. per cent, rice diet 290 mg. per cent. Comparable information is not available in the healthy subjects.

Liver Function. Following the observation that a decreased percentage of esterified cholesterol was frequently observed in patients on the rice diet, studies of liver function were made utilizing the usual clinical tests. Although during the control period normal results were obtained in twenty-five patients, approximately 20 per cent of these patients developed abnormal bromsulfthalein retention (over 10 per cent of dye retained at forty-five minutes*), and 25 per cent abnormal thymol turbidity (over 6.0 units) while on the basic rice diet (Diet IV). The two findings usually did not occur in the same patients. Abnormal cephalin flocculation tests developed in only two patients. Abnormalities of serum bilirubin and alkaline phosphatase levels or urinary urobilinogen excretion were not observed.

Sensitivity to dicumarol was abnormally great in seven of nine patients studied on the rice diet. Prothrombin times[19] forty-eight hours after an oral dose of 300 mg. of dicumarol exceeded those of a group of hypertensive subjects who received the drug while on the control diet. (Table VI.)

COMMENTS

Patients with essential hypertension exhibit more severe arteriosclerosis than normotensive

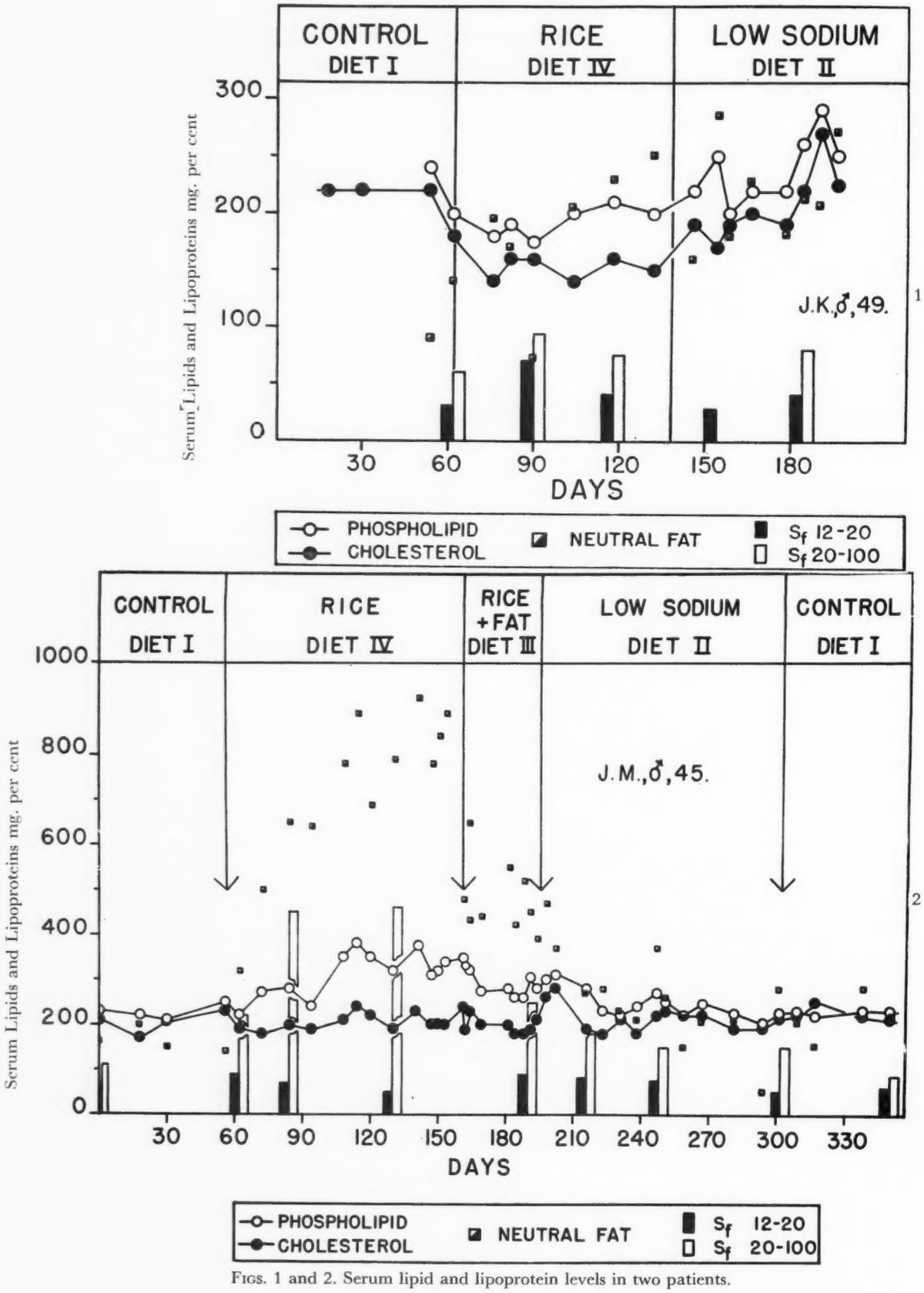
* Dose of dye 5 mg./kg. of body weight.

TABLE V

SERUM LIPOPROTEIN LEVELS WITH CONCOMITANT SERUM LIPID LEVELS DURING PERIODS OF CONTROLLED INTAKE OF FAT AND CHOLESTEROL

Patient	Diet No.	Time (wk.)	Intake (gm./day)		S_f 12–20 (mg. %)	S_f 20–100 (mg. %)	Total Cholesterol (mg. %)	Free Cholesterol (mg. %)	Lipid Phosphorus (mg. %)	Neutral Fat (mg. %)
			Fat	Cholesterol						
A. B.	I	6	85	1.0	40	...	222	58	8.5	110
	IV	5	3	0.0	37	...	157	43	8.6	110
T. B.	I	6	85	1.0	185	161	258	92	13.5	470
	IV	6	3	0.0	120	167	240	82	11.2	350
H. C.	I	6	85	1.0	48	...	202	54	7.8	240
	IV	6	3	0.0	33	...	148	43	7.0	300
G. D.	I	6	85	1.0	40	76	208	68	9.3	150
	II	8	55	0.1	56	131	217	60	10.6	350
	IV	7	3	0.0	45	126	199	60	9.2	270
B. F.	I	6	85	1.0	94	116	212	63	8.9	100
	II	3	55	0.1	97	95	199	60	8.6	220
	IV	2	3	0.0	107	284	220	74	11.4	470
A. H.	I	6	85	1.0	24	...	242	62	9.6	230
	IV	10	3	0.0	37	...	188	74	11.1	510
J. K.	I	6	85	1.0	33	62	182	54	8.0	140
	II	7	55	0.1	41	82	229	68	10.2	230
	IV	8	3	0.0	40	126	163	48	8.3	220
A. Ma.	I	2	85	1.0	88	...	295	81	13.1	200
	IV	18	3	0.0	143	...	230	88	14.4	620
B. M.	I	6	85	1.0	29	...	228	63	9.4	240
	IV	6	3	0.0	108	...	227	76	12.6	700
I. M.	I	6	85	1.0	59	...	238	64	10.7	130
	IV	6	3	0.0	86	...	187	52	9.1	220
J. M.	I	6	85	1.0	69	109	207	59	9.0	160
	II	8	55	0.1	75	148	233	74	9.9	250
	III	1½	60	0.1	101	226	208	60	11.1	450
	IV	4	3	0.0	66	450	198	70	12.3	650
G. P.	I	2	85	1.0	24	...	171	47	7.4	200
	IV	4	3	0.0	29	...	164	44	7.9	190
J. R.	I	6	85	1.0	69	103	237	77	10.2	330
	II	10	55	0.1	69	82	220	70	9.6	330
	IV	3	3	0.0	54	219	215	76	9.8	320
L. S.	I	2	85	1.0	41	41	160	50	7.3	190
	II	2	55	0.1	41	69	172	44	7.3	150
	IV	3	3	0.0	47	114	154	57	6.8	310
M. Si.	I	6	85	1.0	33	59	140	44	6.4	40
	II	4	55	0.1	54	58	187	52	8.5	180
	IV	5	3	0.0	55	88	162	48	7.8	180
A. W.	I	6	85	1.0	29	...	200	56	8.5	140
	IV	5	3	0.0	53	...	175	48	9.0	170
D. W.	I	6	85	1.0	52	150	215	58	10.0	340
	II	1.5	55	0.1	58	155	233	65	9.6	280
	IV	5	3	0.0	50	226	216	65	10.4	350
J. W.	I	6	85	1.0	45	80	231	72	9.4	200
	IV	7	3	0.0	62	138	262	80	8.1	50
M. W.	I	6	85	1.0	114	114	274	78	11.8	200
	II	4	55	0.1	107	137	208	78	10.3	380

Key to diets: I, control diet; II, special low sodium diet; III, modified rice diet; IV, rice diet.



FIGS. 1 and 2. Serum lipid and lipoprotein levels in two patients.

individuals of the same age and sex.[20] Dietary treatment is often recommended for these patients in the hope that either the elevated blood pressure, the arteriosclerotic process, or both will be benefited. A controlled experimental approach has been utilized in this and

TABLE VI
DICUMAROL SENSITIVITY *

	Undiluted Plasma	Diluted Plasma (1–8)
	Prothrombin Time in Seconds	
Ten patients on control diet:		
Before	19	43
48 hr.	23	47
Nine patients on rice diet:		
Before	23	52
48 hr.	42	112

* Prothrombin times before and forty-eight hours after single oral dose of 30 mg. of dicumarol.

the related investigations[1] in order to elucidate the clinical and metabolic effects of various dietary restrictions in patients with hypertension. Patients have been studied on diets with three degrees of restriction of fat and cholesterol intake.

The fat intake levels of the restricted diets ranged from 3 to 55 gm. per day and the cholesterol intake levels from 0 to 0.25 gm. per day. The salt and protein contents of the diets were additional variables. With respect to sodium chloride intake no significant changes in serum lipid pattern were produced by the addition of 0.5 to 3 gm. of sodium chloride per day to the low sodium regimens (Diets II, III or IV) of five patients. The influence of variations in protein intake has not been fully assessed. No effect on the serum lipid levels was produced by raising the protein content of the supplemented rice diet (Diet III) to 40 and to 80 gm. per day. The rice diet (IV) is unusual in the very character of its foods since it contains only rice, fruits and fruit juice and sugar. Therefore it is possible that some unrecognized deficiency contributed to the results obtained with this diet.

Partial or nearly complete restriction of dietary fat and cholesterol under the conditions of these studies failed to reduce serum lipid and lipoprotein levels in any patient below the normal range of values. The question is raised as to how these serum concentrations are maintained in the absence of direct dietary contributions of fatty acids and cholesterol.

Unless a starvation regimen be imposed the restriction of dietary fat implies an increase in the carbohydrate intake. Chaikoff[21] and Stetten[22] and their co-workers have shown in experiments with rats that a large proportion (perhaps one-third) of ingested glucose is transformed into fat before utilization. This transformation, which is at least partly under the control of insulin, is carried on actively at normal and high levels of carbohydrate intake and regardless of the absence of fat or protein from the diet.

Since the storage capacity of the body for carbohydrate is limited, conversion of carbohydrate into fat is to be expected when food intake exceeds energy requirements. Evidence for such a conversion is available in our studies. A comparison of changes in total body water (measured by means of antipyrine*) with changes in body weight occurring on the rice diet (IV) revealed that in eleven of the seventeen patients studied there was a greater loss of water than of weight. The magnitude of these increases ranged from 1 to 10 kg. over periods of three to fifteen weeks on the rice diet. This paradox presumably resulted in part from increases in the body fat. Confirmatory evidence is provided by the finding of a postabsorptive respiratory quotient* slightly greater than 1.0 in one subject who was gaining weight while losing body water. Such a respiratory quotient is generally presumed to indicate the transformation of carbohydrate into fat.

The continuation of normal serum cholesterol concentrations after elimination of the dietary cholesterol intake is probably also due to an active mechanism for endogenous synthesis. Abundant supplies of the known precursors of cholesterol are available from the metabolic pools of small organic molecules in the body. Abell and Kendall[23] in this laboratory have shown that the excretion of cholesterol in the feces is not greatly reduced in patients on the

* For these measurements we are indebted to the New York University Research Service, Goldwater Memorial Hospital. Drs. M. Dunning and E. Y. Berger performed the studies of total body water and Dr. Morton Galdston determined respiratory quotients in selected patients.

rice diet. (Table VII.) Four patients excreted amounts (0.3 to 0.9 gm. per day) of total digitonin-precipitable sterols ranging from 50 to 125 per cent of their excretion on the control diet. The average change on the restricted diet was a decrease of only 20 per cent in fecal sterol

TABLE VII
FECAL STEROL EXCRETION DURING CONTROL AND RICE DIETS

Patient	Weeks on Rice Diet	Total Digitonin-precipitable Sterols (mg./day)		
		Control (I)	Rice (IV)	Change (%)
F. S.	28	430	300	−30
B. M.	6	480	600	+25
H. C.	6	1150	920	−20
A. W.	11	730	350	−53
	Average	700	540	−23

excretion despite the fact that dietary sterol intake decreased from 1 gm. per day on the control diet[1] to 0.1 gm. per day of plant sterols (digitonin-precipitable) on the rice diet (IV). This study provides strong evidence of an active synthesis and excretion of cholesterol in the body when the exogenous supply of preformed cholesterol is cut off.

There was a marked variation in the response of different individuals to the dietary restrictions. The changes in concentration of the serum lipids and lipoproteins following restriction of dietary fat and cholesterol cannot be predicted for any given patient. The type of change observed cannot be correlated with the degree of elevation of the blood pressure, with the response of the blood pressure to treatment, with the presence or absence of overt arteriosclerosis, or with changes in body weight.

In these studies changes in cholesterol intake did not have any effect distinct from that resulting from fat restriction. The special low sodium diet (Diet II) which provided 55 gm. of fat but *only 40 mg. of cholesterol* daily did not significantly change the serum lipid or lipoprotein levels from the values observed on the control diet (Diet I), which contained 85 gm. of fat and 1 gm. of cholesterol daily. Our observations indicate that it is the restriction of dietary fat rather than cholesterol which affects the metabolism of the serum cholesterol and other lipids. This finding is in agreement with the results of Keys[24] and of Hildreth et al.[25]

It has been shown that patients on the rice diet frequently develop abnormal responses to some of the tests used to evaluate liver function. In a previous paper[1] these abnormalities were considered to be indicative of a mild disorder of liver function which might also be responsible for the changes in the serum lipid pattern observed during restriction of dietary fat. This point of view has now been modified. With one exception the abnormal results in thymol turbidity tests occurred only in patients who exhibited neutral fat lipemia on the rice diet. We have observed that transient elevation of the thymol turbidity test also occurs during alimentary lipemia. Kunkel and Hoagland[26] have reported that false-positive thymol turbidity tests are associated with the lipemia occurring in the nephrotic syndrome. Thus it seems probable that the elevations of thymol turbidity observed in this study are related to changes in the serum lipoproteins involved in the reaction with thymol rather than to disordered function of the liver.

The hypersensitivity to dicumarol noted in this investigation was probably due to faulty absorption of vitamin K occasioned by decreased absorption of fat on the restricted diet. The hypersensitivity could be abolished either by adding fat to the diet or by administering 20 mg. per day of a water-soluble preparation of vitamin K.

The decline in the percentage of cholesterol in the ester fraction and the occasional finding of increased bromsulfthalein retention thus remain as the only indicators of hepatic dysfunction in patients on the rice diet. Although altered metabolic processes in the liver probably contribute to the observed changes in serum lipid and lipoprotein patterns, there is no cogent argument for clinically important liver damage.

SUMMARY AND CONCLUSIONS

Controlled observations of serum lipid and lipoprotein levels have been made in a series of hospitalized patients with severe essential hypertension undergoing both partial (twenty-three patients) and practically complete (forty-four patients) restriction of dietary fat and cholesterol. There is no information to indicate that the observations reported here are peculiar to the hypertensive individual.

Three major findings resulted from this investigation: (1) The restriction of dietary fat

to 3 gm. per day and elimination of cholesterol intake did not reduce the serum lipid or lipoprotein levels in any patient below the normal range of values. Compensatory metabolic mechanisms exist for maintaining the serum lipid and lipoprotein concentrations when lipid is not available in the diet. Carbohydrate and protein appear to be ready sources for endogenous synthesis of the lipids present in the serum. (2) The results of drastic dietary restriction of fat and cholesterol showed great variability among patients in the effects on the serum lipid patterns. Serum cholesterol ester levels usually declined with restriction of daily fat intake below 40 gm. Free cholesterol and lipid phosphorus concentrations showed no consistent change. However, one-fifth of the patients undergoing such restriction exhibited a lipemia chiefly marked by elevation of the serum neutral fat. Data on serum lipoproteins showed that the dietary restriction did not significantly alter the concentration of the S_f 12–20 class of particles and that substantial increases in the S_f 20–100 class were provoked. The response of the serum lipids and lipoproteins to restriction of dietary fat was not predictable for any given patient. The type of change observed was not correlated with the severity of the hypertension or with the presence or absence of arteriosclerotic complications. (3) The restriction of dietary fat rather than the restriction of dietary cholesterol is responsible for the observed alterations of the serum concentrations of cholesterol and other lipids.

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The Effects of Sitosterol on Serum Lipids*

MAURICE M. BEST, M.D., CHARLES H. DUNCAN, M.D., EDWARD J. VAN LOON, PH.D., *and* JOAN D. WATHEN, B.S.

Louisville, Kentucky

IN 1951 Peterson reported that the addition of mixed soybean sterols to a cholesterol-enriched diet fed to chicks prevented the hypercholesterolemia which otherwise occurs on a high cholesterol diet.[1] On the basis of this observation he proposed that the absorption of cholesterol is interfered with by one or more of the constituents of soybean sterol mixtures, most likely sitosterol. That sitosterol might interfere with reabsorption of cholesterol secreted into the intestinal tract in mice had previously been suggested by Sperry and Bergmann.[2]

Stimulated by Peterson's report and the growing body of evidence linking cholesterol with atherosclerosis[3] a number of investigators have been exploring the effects in man of the administration of soy sterols, with conflicting results reported.[4,5] Unreported studies in this laboratory noted a hypocholesterolemic effect in man of a soy sterol mixture containing approximately 80 per cent gamma-sitosterol, the greater part of the remainder being stigmasterol.

In a preliminary report[6] we summarized the effects of the administration of beta-sitosterol (a stereoisomer of the gamma-sterol) up to eighteen weeks on nine patients on an unrestricted diet. The sterol used was derived from tall oil or cottonseed oil and contained 98 per cent beta-sitosterol. In all patients there was a reduction in serum total cholesterol, the mean fall ranging from 6.7 to 20.0 per cent of the control level. A reduction in the ratio of total cholesterol to lipid phosphorus was also noted.

Sufficient data have now been obtained in fourteen patients to permit evaluation of the effects of the prolonged administration of beta-sitosterol on serum cholesterol and other lipid fractions.

METHODS

Fourteen subjects (Table 1) were studied for periods ranging from thirteen to sixty-four weeks, the mean period of observation being forty weeks. Twelve subjects had elevated serum cholesterol levels not associated with hypothyroidism, diabetes mellitus or the nephrotic state. The remaining two volunteers were "normal." A major factor in the selection was the ability and willingness of the subjects to cooperate and adhere to the prolonged schedule of treatment.

Six to 8 gm. of beta-sitosterol† was administered orally immediately before the ingestion of food, the usual total being 20 to 25 gm. per day. As much as 50 gm. per day has been administered on occasion. A placebo preparation, similar in appearance, taste and consistency, was administered for one or more periods to each patient. At no time did the patient know whether he was taking sitosterol or a placebo and, with the exception of the three faculty members included in the study (H-1, H-2, H-4), none was aware that a placebo was used. This precaution was taken to avoid possible influence of such knowledge on the patient's selection of diet, particularly with regard to fat and cholesterol content. There was no restriction as to the amount or type of diet.

Each patient was seen at one or two week intervals, his weight recorded, and a fasting specimen of blood drawn at approximately 9 A.M. The blood was allowed to clot and the serum separated by centrifugation. If there was any evidence of hemolysis the specimen was discarded. Total cholesterol was determined by the method of Abell,[7] lipid phosphorus by the method of Zilversmit,[8] and total lipid by the method of de la Huerga.[9] Multiplication of lipid phosphorus by 25 permits its expression as phospholipid. That portion of the total lipid not

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accounted for as phospholipid or cholesterol was designated neutral fat.[10]

In seven subjects the effect of sitosterol on serum lipoproteins, as determined by ultracentrifuge, was studied. At intervals during both control and treatment periods a sufficient amount of blood was collected from these subjects to permit this additional analysis. The portion of the serum specimen for ultracentrifugal analysis was refrigerated and shipped air mail to Indianapolis. Analysis was performed at a solution density adjusted to 1.063, and a template employed to facilitate the calculations.[11]

TABLE I

CLINICAL DATA OF SUBJECTS TREATED WITH SITOSTEROL

Patient	Age and Sex	Observation (weeks)	Sitosterol Therapy (weeks)	Remarks
A-6	43, M	34	28	Xanthoma tuberosum (confirmed by biopsy)
A-5	43, M	44	36	Acute myocardial infarction six weeks prior to treatment; angina pectoris
A-4	41, M	48	40	Acute myocardial infarction one year prior to treatment; angina pectoris
H-7	77, F	56	52	Acute myocardial infarction three years prior to treatment; angina pectoris
A-3	51, F	28	20	Xanthelasma
H-6	50, M	56	32	Acute myocardial infarction nine years prior to treatment; obesity
H-8	40, F	64	52	Undiagnosed disease one year prior to treatment (hypertension, anasarca, proteinuria, abnormal pattern of serum proteins by electrophoresis and acute arteritis by biopsy; duration four months)
H-5	33, M	60	52	Labile hypertension
A-2	41, M	22	16	Acute myocardial infarction eighteen months prior to treatment; xanthelasma
H-4	58, M	62	56	Peripheral arterial insufficiency
H-3	65, M	13	8	Acute myocardial infarctions one, four and five years prior to treatment; angina decubitus
A-1	34, F	34	28	Idiopathic hyperlipemia
H-2	43, M	24	8	Obesity; otherwise "normal"
H-1	46, M	22	8	"Normal"

RESULTS

Changes in serum lipids consequent to sitosterol administration in a representative patient (H-6) are shown in Figure 1. During each of the three periods of sitosterol administration serum total cholesterol and total lipid were maintained at levels significantly below the mean control values. The substitution of a placebo preparation during the first two control periods was accompanied by a return to the pretreatment range. During the final control period the patient received neither sitosterol nor a placebo, and again serum lipids returned to the pretreatment range. The lack of consistent effect on lipid phosphorus in this patient is considered representative; most other patients, however, demonstrated a more consistent fall in neutral fat during sitosterol administration.

The effects of sitosterol administration on the various serum lipids in the fourteen patients

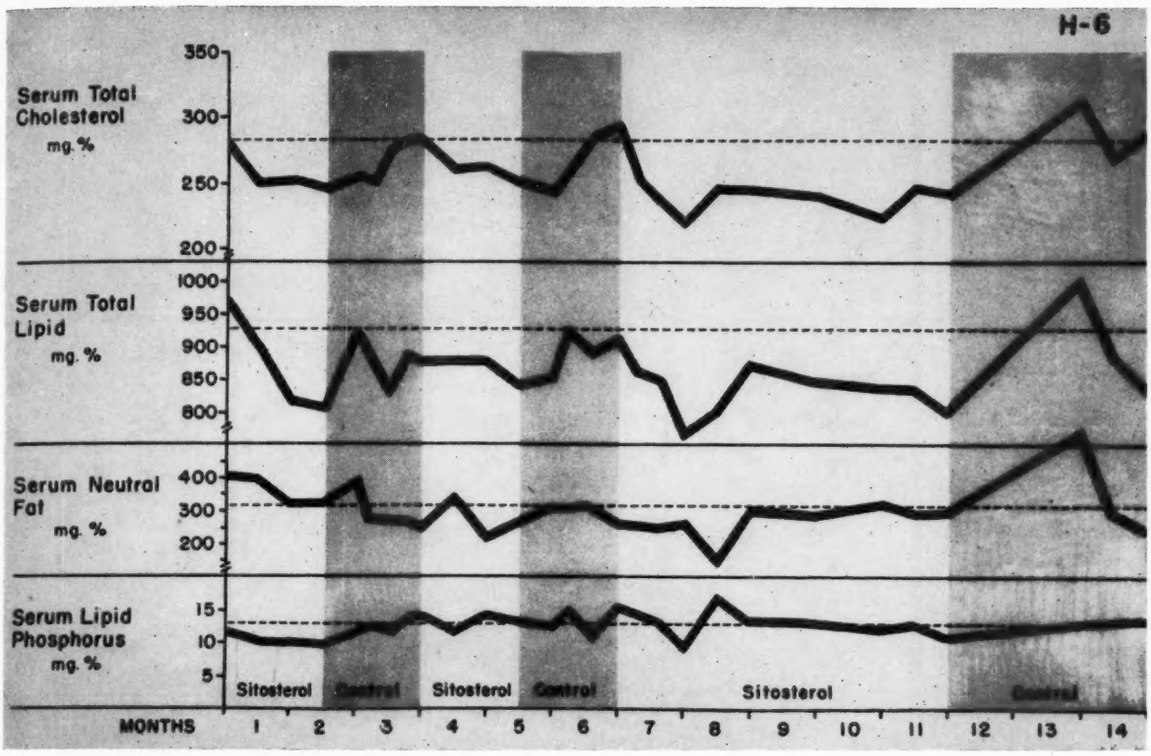

FIG. 1. Effects of repeated administration of sitosterol; effects of sitosterol on the various serum lipids of a representative hypercholesterolemic patient. Broken lines indicate mean control.

studied are presented in composite dot diagrams (Figs. 2, 3, 4, 5 and 6) constructed in a similar manner. The per cent deviation from mean control values is represented on the vertical axis. At the left each dot represents one control determination, expressed as per cent deviation from the mean control value for that subject. To the right of the broad vertical line the data are expressed in terms of months, each dot representing the mean of the two to four determinations made during the month. The mean control level is represented by the broken line; the solid line represents the mean effect of sitosterol administration. The two patients (A-1 and A-6) with pronounced hyperlipemia displayed unusual spontaneous fluctuations in serum lipids and are designated by triangles.

The administration of beta-sitosterol is accompanied by a consistent fall in serum total cholesterol. (Fig. 2.) This effect is manifested by the end of one week, and a further decline occurs during the succeeding several weeks. The effectiveness of sitosterol in lowering serum cholesterol is sustained throughout the period of study, there being no indication of a tendency to "escape."

The degree, approximately 20 per cent, and consistency of the reduction in serum total lipid (Fig. 3) are similar to those of cholesterol. Since serum cholesterol constitutes only about one-third of the total lipid, it is evident that one or more other serum lipids must be decreased following administration of sitosterol.

A less pronounced and less consistent effect was observed on serum lipid phosphorus. (Fig. 4.) The variability of the lipid phosphorus during both control and treatment periods can be seen to be appreciably greater than that of either total cholesterol or total lipid.

The remainder of the total lipid not accounted for as phospholipid or cholesterol has been designated neutral fat. The mean reduction in neutral fat (Fig. 5) is in general comparable to that in cholesterol. An even greater degree of variability of neutral fat is apparent.

The ratio of serum total cholesterol to lipid phosphorus has been described as being relatively constant.[12] The variability in control values of this ratio (Fig. 6) is therefore somewhat unexpected. Some reduction of the total cholesterol/lipid phosphorus ratio resulted from sitosterol administration, a reflection of the greater reduction of cholesterol as compared to that of lipid phosphorus.

The mean levels of each of the various serum

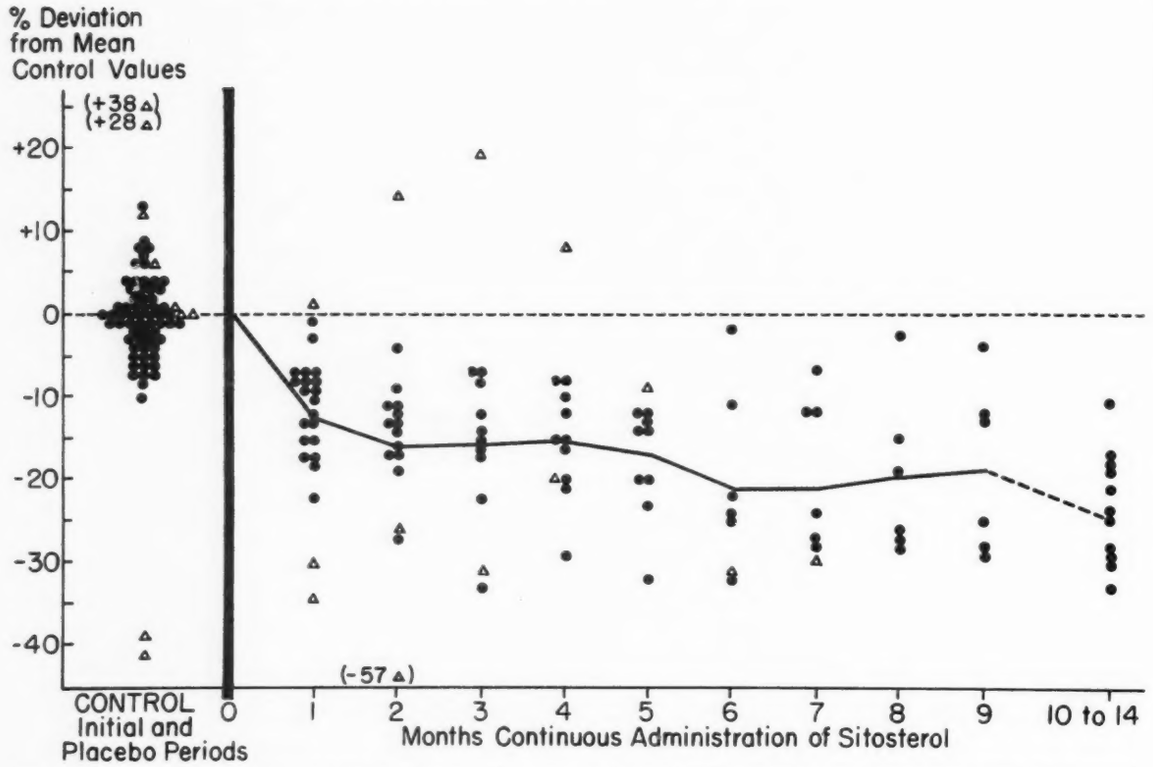

FIG. 2. Per cent change; serum total cholesterol (fourteen subjects). Effect of sitosterol on serum total cholesterol. The triangles designate values in two patients (A-1 and A-2) with pronounced hyperlipemia (see text).

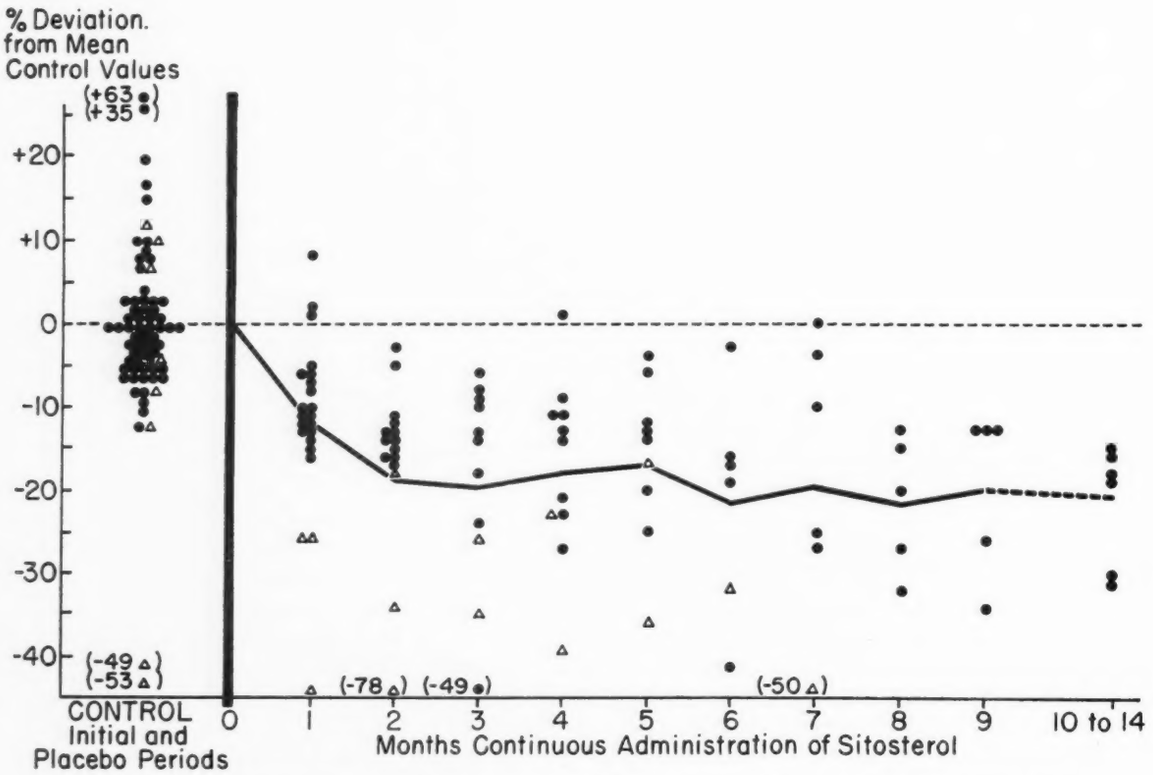

FIG. 3. Per cent change; serum total lipid (thirteen subjects). Effect of sitosterol on serum total lipid.

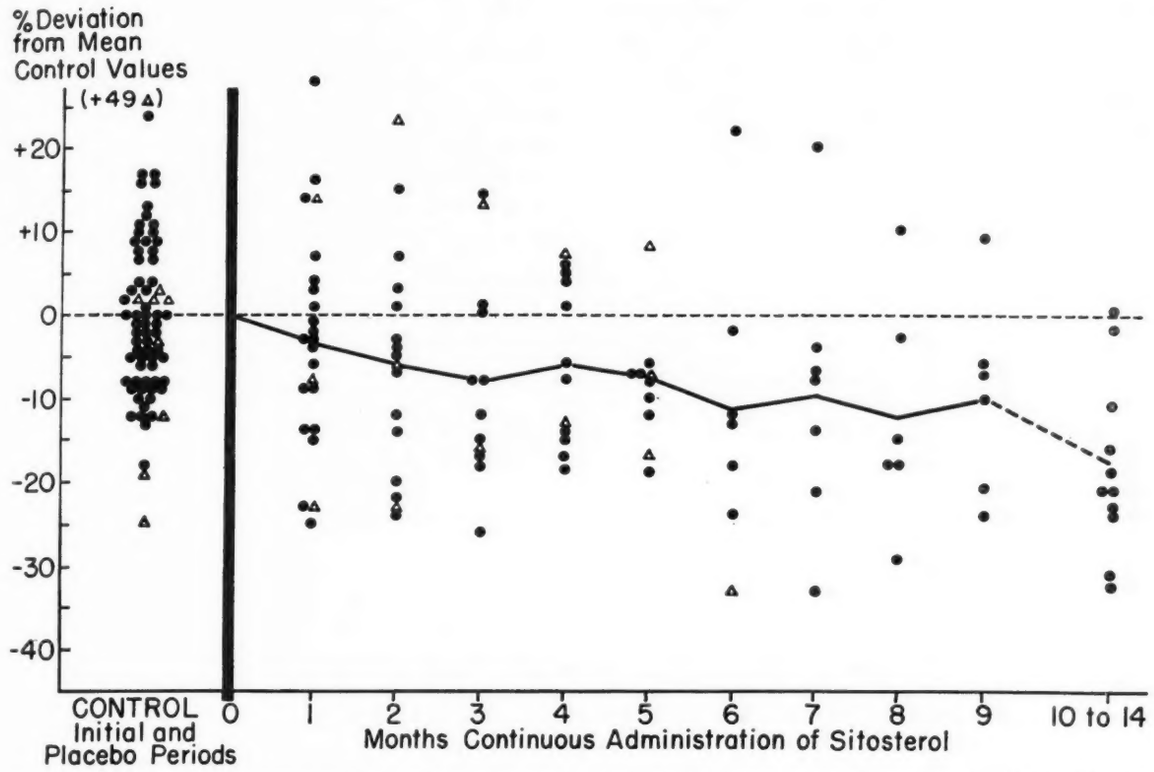

FIG. 4. Per cent change; serum lipid phosphorus (fourteen subjects). Effect of sitosterol on serum lipid phosphorus.

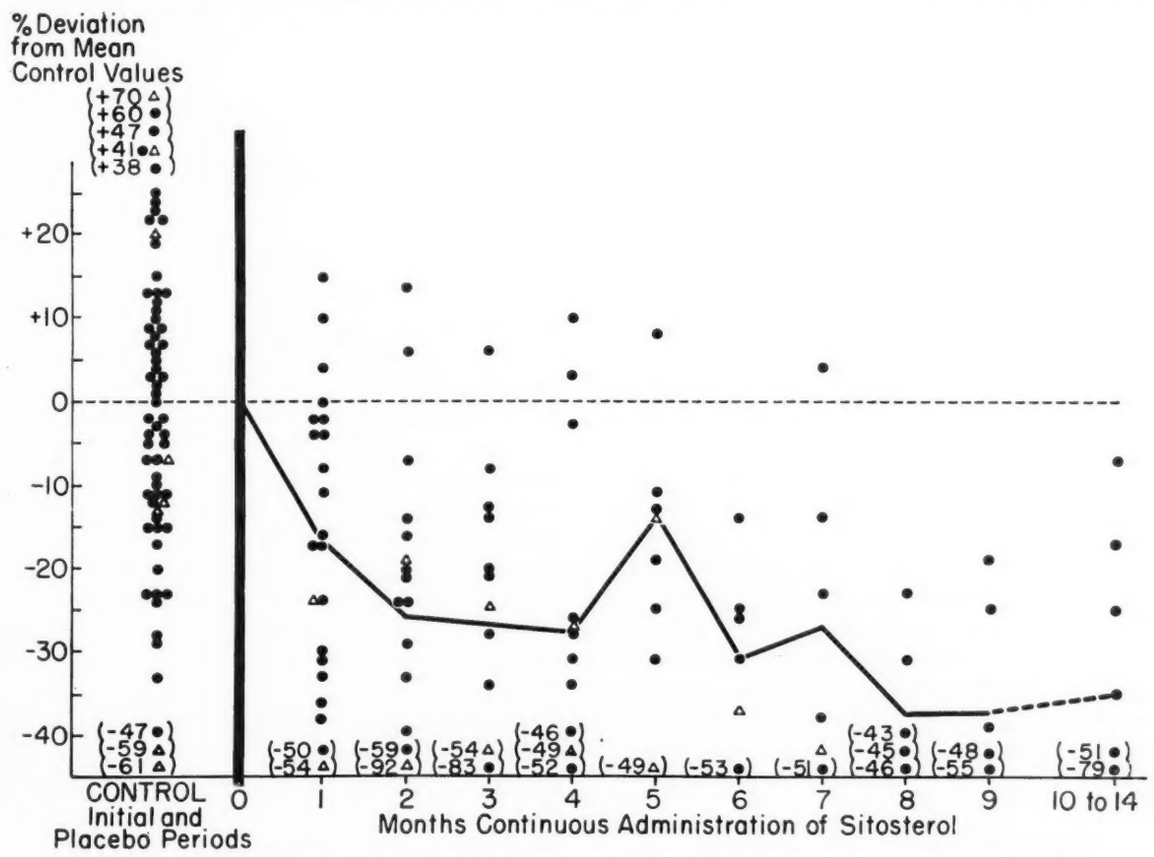

FIG. 5. Per cent change; serum neutral fat (thirteen subjects). Effect of sitosterol on serum neutral fat.

lipids during control periods and periods of sitosterol administration are tabulated in Table II. All determinations of serum lipids are included in the data presented except those made during the two-week period immediately following discontinuation of sitosterol. These values were omitted in order to minimize any possible persistent sitosterol effects on the control values. Data on serum total lipid and neutral fat are missing for subject H-8, whose serum displayed a peculiar clotting tendency that made routine determination of total lipid impractical.

The subjects are listed in order of decreasing control level of serum cholesterol. It can be seen that all patients displayed a fall in cholesterol; the fall ranged from 28.8 per cent of the control level in patient A-5 to 6.5 per cent of the control value in subject H-2. It will be observed that in general the higher the control level of cholesterol the greater the fall during sitosterol administration, not only in absolute values but in terms of per cent as well. Thus the twelve hypercholesterolemic patients experienced a mean fall of 16.0 per cent while the two "normal" subjects had a mean fall of 6.8 per cent.

The two patients with pronounced hyperlipemia, designated by triangles in Figures 2 to 6, deserve special comment. One subject, A-6, displayed marked elevation of all the lipid fractions determined, with a mean control serum total cholesterol of 843 mg./100 ml. The other subject, A-1, displayed an increase chiefly in neutral fat, her mean control cholesterol being 224 mg./100 ml. In both there were wide fluctuations in serum lipid levels during both control and treatment periods (Table II). Although the mean fall in cholesterol and other lipids displayed by these two subjects is comparable to that of the other patients, the wide fluctuations make interpretation difficult and more observations will be needed to evaluate fully the effects of sitosterol in such hyperlipemic subjects.

The mean levels of serum lipoproteins of the S_f classes determined during control periods and periods of sitosterol administration in seven patients are shown in Table III. Although a trend toward lower levels of S_f 3–100 lipoproteins during the administration of sitosterol is apparent, this effect is much less consistent than that on serum cholesterol and total lipid.

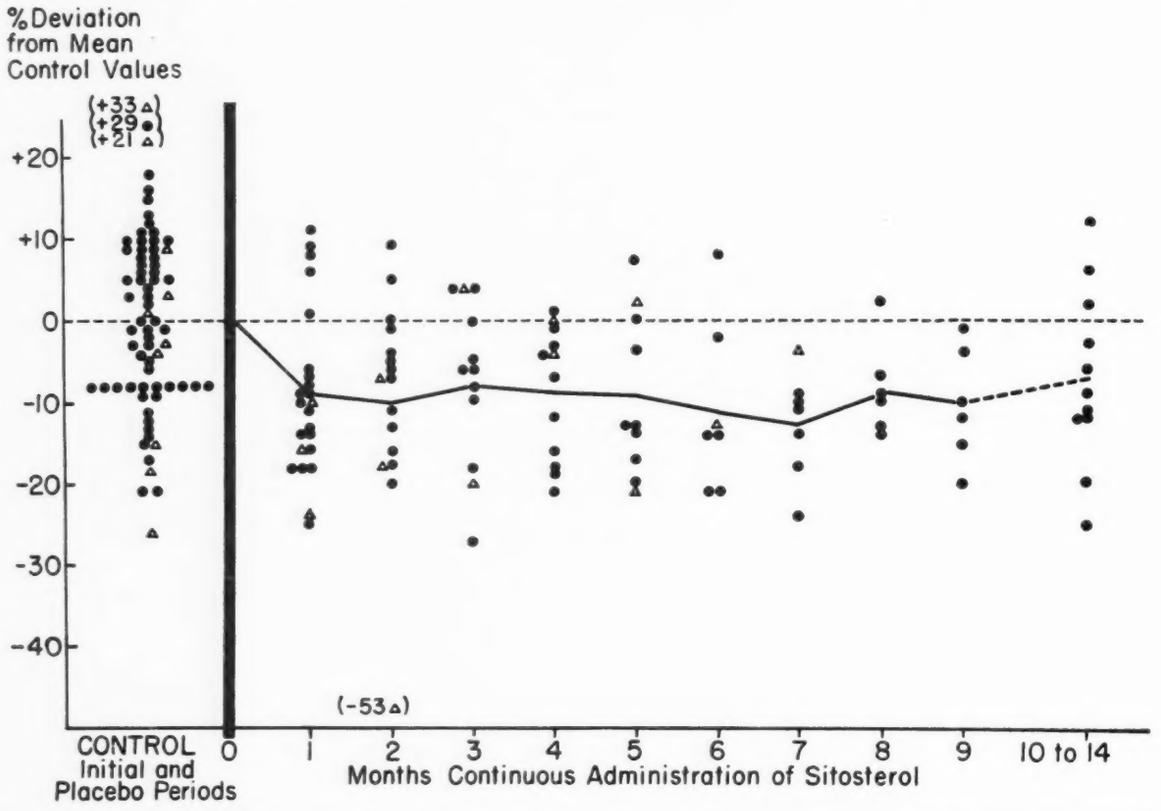

FIG. 6. Per cent change; ratio serum total cholesterol/lipid phosphorus. Effect of sitosterol on serum total cholesterol/lipid phosphorus ratio.

COMMENTS

A sustained lowering of serum total cholesterol results from the prolonged administration of beta-sitosterol. A concomitant reduction in serum total lipid, neutral fat and, to a lesser degree, lipid phosphorus occurs. The employment of a placebo during control periods and the failure of any of the patients to lose weight during the period of study, would seem to eliminate any possibility that the effects observed were due to dietary modification. The number of determinations performed in each patient allows for the recognized variability in serum cholesterol.[13]

Studies with animals have done much to explain the probable mechanism of the hypo-

TABLE II

EFFECTS OF SITOSTEROL ON SERUM LIPIDS

(Expressed in mg./100 ml.)

Patient		Total Cholesterol		Lipid Phosphorus		Neutral Fat		Total Lipid		TC/LP Ratio	
		Control	Sitosterol	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol
A-6	Mean	843	614	33.5	28.1	3092	2264	4772	3581	24.1	21.8
	S.D.	56	84	0.9	2.9	542	290	500	413	0.9	1.9
A-5	Mean	361	257	17.5	13.9	457	283	1254	889	20.4	18.7
	S.D.	26	12	1.6	1.2	74	106	123	138	1.1	1.2
A-4	Mean	330	281	14.7	13.5	349	278	1019	899	22.5	20.9
	S.D.	19	15	1.3	0.1	52	46	73	34	1.2	1.9
H-7	Mean	297	237	14.8	13.3	269	177	937	743	20.3	18.0
	S.D.	13	14	1.7	2.5	54	60	26	56	2.9	1.4
A-3	Mean	286	253	16.1	14.3	213	193	902	804	17.7	17.7
	S.D.	17	11	1.3	1.9	38	57	75	36	1.3	1.7
H-6	Mean	285	244	12.8	12.3	314	290	927	839	22.6	20.6
	S.D.	13	11	1.2	1.4	106	43	103	22	2.6	2.1
H-8	Mean	276	214	15.1	12.1	....	....	....	....	18.4	17.6
	S.D.	4	27	1.2	1.1	....	....	....	....	1.8	1.5
H-5	Mean	273	235	14.7	13.6	412	403	1054	965	19.0	17.6
	S.D.	10	11	2.2	1.5	47	48	73	80	3.6	1.8
A-2	Mean	264	243	12.6	13.0	208	180	788	749	21.1	18.9
	S.D.	7	11	1.5	0.4	38	41	24	31	2.1	1.1
H-4	Mean	261	233	12.1	12.9	338	235	902	790	21.8	18.4
	S.D.	16	17	1.6	1.3	86	34	64	52	2.7	1.7
H-3	Mean	260	229	12.2	11.4	357	298	920	813	21.5	20.3
	S.D.	11	14	1.1	5.0	57	1	43	3	2.2	1.8
A-1	Mean	224	206	12.6	13.1	1520	664	2059	1198	17.8	15.2
	S.D.	68	43	3.1	1.9	739	259	870	344	4.0	2.9
H-2	Mean	215	201	11.4	13.8	291	212	791	758	18.9	14.9
	S.D.	10	9	1.0	1.1	42	94	37	131	1.5	0.9
H-1	Mean	196	182	10.7	10.2	290	240	752	688	18.6	17.9
	S.D.	11	7	1.3	1.4	73	67	57	23	2.2	3.2

cholesterolemic effect of sitosterol. The suggestion that sitosterol acts by interfering with the absorption of cholesterol from the digestive tract[1,2] has been confirmed by Hernandez using the technic of thoracic duct cannulization in rats.[14,15] He fed C^{14}-labeled cholesterol, alone and in conjunction with either beta-sitosterol or mixed soy sterols, and observed that addition of the plant sterols resulted in a pronounced decrease in the C^{14} recovered in the thoracic duct lymph.

TABLE III
EFFECT OF SITOSTEROL ON SERUM LIPOPROTEINS

Patient	Sf 3–10 (gm./100 ml.)		Sf 10–30 (gm./100 ml.)		Sf 30–100 (gm./100 ml.)		Total Cholesterol (mg./100 ml.)	
	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol
A-5	.39	.34	.17	.08	.37	.12	357	272
A-4	.46	.28	.06	.05	.09	.06	360	266
H-7	.21	.31	.07	.03	.01	.01	282	234
A-3	.70	.28	.12	.03	.09	.12	298	265
H-6	.43	.37	.03	.10	.08	.07	304	253
A-2	.27	.25	.02	.07	.01	.01	270	238
H-4	.44	.29	.10	.05	.12	.07	261	241

The structural formulas of cholesterol and beta-sitosterol are quite similar, differing only in the presence of an ethyl group on carbon-24 of sitosterol. Both possess a free hydroxyl group on carbon-3. It is by means of this carbon-3 hydroxyl group that cholesterol, in the presence of bile salts and pancreatic esterase, combines with fatty acids to form cholesterol esters. That soy sterols under the same conditions also form esters has recently been shown by Swell and coworkers.[16]

Esterification of the greater part if not all of the cholesterol absorbed occurs at some point between its introduction into the gut and its arrival in the lymph. Peterson has observed that when cholesterol is fed as an ester its rate of absorption is decreased rather than increased.[17] This observation is best understood if esterification is considered as a step in the transport mechanism by which cholesterol is absorbed. Thus prior esterification would be expected to impede rather than to facilitate absorption.

In view of these considerations it is suggested that sitosterol interferes with cholesterol absorption by competing for esterification, a step in the transport mechanism by which cholesterol is absorbed. Schoenheimer failed to demonstrate by chemical methods any absorption of sitosterol, and it was long considered to be essentially non-absorbable.[18] Recently Gould, employing tritium-labeled sterols, has restudied the absorption of cholesterol and sitosterol.[19] He observed that beta-sitosterol was absorbed, though much less readily than cholesterol. Sitosterol also disappeared from the blood much more rapidly than cholesterol and did not accumulate in the body. The demonstration that sitosterol is absorbed, though poorly, perhaps lends support to the concept that it acts by competing with cholesterol for absorption.

It seems probable that sitosterol interferes with the absorption of the cholesterol excreted in the bile as well as that present in the diet since both are introduced into the intestine in the free state. That the results of sitosterol administration are not identical with those of restriction of dietary cholesterol (a measure that does not consistently lower serum cholesterol unless accompanied by restriction of dietary fat[20]) is most likely due to its effect on biliary cholesterol.

The administration of sitosterol is accompanied by a significant lowering of serum neutral fat. This is presumably a secondary effect to the lowering of serum total cholesterol, an appreciable part of which is present in complex combinations also containing neutral fat. The possibility remains, however, that sitosterol in the dosage administered might interfere also with fat absorption, leading to lower levels of serum neutral fat and contributing to the reduction of serum cholesterol. Results of current studies of the effect of sitosterol on fat absorption may serve to clarify the mechanism by which sitosterol lowers serum neutral fat.

Gofman and coworkers have been concerned with the physicochemical state of the serum lipids as determined by the analytical ultracentrifuge and as expressed in Svedberg units of migration (S_f). They report that restriction of dietary fat results in a reduction of the serum levels of S_f 12–100 lipoproteins, classes which they consider to be particularly concerned with atherosclerosis.[21] The administration of sitosterol also appears to effect a lowering of these classes of lipoproteins.

The amount of sitosterol employed in these studies, 20 to 25 gm. per day, was largely empiric. As little as 10 gm. per day has been noted to have a hypocholesterolemic effect; higher dos-

age, up to 50 gm. per day, appeared to have a more pronounced effect, but optimal dosage has not yet been determined.

Attempts to lower or otherwise alter the serum lipids and lipoproteins have been the natural outgrowth of the cholesterol concept of atherogenesis. The changes in serum lipids and lipoproteins resulting from sitosterol administration, on theoretical grounds, may be considered desirable in atherosclerotic states. The absence of any toxic or adverse side effects of sitosterol permits continuation of these studies to evaluate its effect on atherosclerosis in man.

SUMMARY

1. The effects of the plant sterol, beta-sitosterol, on serum cholesterol, other lipids and lipoproteins have been studied. Twenty to 25 gm. of sitosterol per day was administered for prolonged periods to fourteen patients on free diets.

2. A sustained lowering of serum total cholesterol results from the prolonged administration of sitosterol. A concomitant reduction in serum total lipid, neutral fat and, to a lesser degree, lipid phosphorus occurs.

3. A trend toward lower levels of S_f 3–10, 10–30 and 30–100 classes of lipoproteins occurs during sitosterol administration but this effect is less consistent than the reduction of serum cholesterol.

4. The effects of sitosterol are attributable to its interference with absorption of cholesterol. They are not identical with those of dietary cholesterol restriction, since sitosterol would seem to reduce absorption of cholesterol present in the bile as well as that present in the diet.

5. It is suggested that sitosterol interferes with cholesterol absorption by competing for esterification, a step in the transport mechanism by which cholesterol is absorbed.

6. The changes in serum lipids and lipoproteins resulting from sitosterol administration are in the direction generally considered desirable in atherosclerosis, and the absence of any toxic or adverse side effects permits its further study in man.

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The Serum Lipid Pattern in Hyperthyroidism, Hypothyroidism and Coronary Atherosclerosis*

RICHARD J. JONES, M.D., LOUIS COHEN, M.D., *and* HOWARD CORBUS, M.D.†
Chicago, Illinois

THE influence of thyroid activity upon the serum lipids has been well documented[1–5] and its clinical usefulness defined.[4–7] With the recent advent of new methods for describing the serum lipids with the analytic ultracentrifuge[8] and filter paper electrophoresis,[9] efforts are again being made to recognize some abnormality in the serum lipid pattern which might distinguish the hyperlipemia of myxedema from the hyperlipemia which may accompany atherosclerosis of the coronary arteries.[10,11] This would seem to be of more than passing interest in view of the current controversy over the relationship of hypothyroidism to atherosclerosis.[12,13]

MATERIAL AND METHODS

Fasting serum was obtained from patients in the University of Chicago Clinics who manifested hypothyroidism, hyperthyroidism or coronary artery disease. Over a three-year period samples were obtained from twenty-five patients, of whom twenty-one were females, with unequivocal hyperthyroidism as yet uncontrolled by therapy. The criteria for hyperthyroidism were the usual clinical signs supported by a basal metabolic rate of more than +20 per cent and/or a serum protein bound iodine level above 8 μg. per cent. Conversion ratios and data on thyroid uptake of I^{131} were obtained through the kindness of Dr. Dwight Clark when necessary.[14] Of these patients, three had an associated diastolic hypertension, one had the anginal syndrome and two had malignant exophthalmos.

In the same period, sera were obtained from seventeen patients with untreated hypothyroidism, of whom ten were females. Thirteen of these patients could be said to have true myxedema by the criteria of Gildea, Man and Peters,[6] including response to therapy. The remaining four were atypical only in that they had an equivocal therapeutic response. Of this total group, two were in congestive heart failure, one was troubled with the anginal syndrome, one patient had hypertension and two more had significant cardiomegaly. Thus approximately one-third of these patients had suggestive evidence of heart disease, although none had an electrocardiographic pattern diagnostic of previous myocardial infarction.

Many patients with coronary artery disease have been followed by periodic analyses of their serum lipids. From this large group were selected a few patients to be matched with the hypothyroid patients as to sex, age and serum cholesterol level. These groups were matched with some difficulty because of the sex difference in the two disorders and a difference in age distribution in the two groups. In order to match the high serum cholesterol levels found in certain hypothyroid patients, we included one man with a previous myocardial infarction and xanthoma tendinosum and tuberosum, and two women who had as yet manifested no evidence of coronary disease but had xanthoma tendinosum in one case and xanthoma planum in the other. One myxedematous woman, age thirty-three, could not be matched with any coronary disease patient, but was matched with a twenty-five-year old woman with comparable cholesterol level and a presumptive family history of coronary disease. The remainder of

* From the University of Chicago, Department of Medicine, Chicago, Ill. Presented in part before the Midwestern Sectional Meeting of The American Federation for Clinical Research in Chicago, Ill., this investigation was supported by a research grant from The National Heart Institute of The National Institutes of Health, Public Health Service.

† Present address: Boston Veterans Administration Hospital, Boston, Mass.

this matched group all had uncomplicated coronary artery disease (as defined by the New York Heart Association Committee of Diagnostic Criteria[15]), either proved myocardial infarction or the anginal syndrome. Sex, serum cholesterol level and age were matched as closely as possible although, as will be seen, certain cases were matched rather loosely as to cholesterol level or age. Except for three cases, which almost cancelled out, the serum cholesterol levels matched within ±31 mg. per cent. The age agreed within six years, except for four pairs. (None of several hundred cases of arteriosclerotic heart disease could be found to match closely with the seventy year old myxedematous man who had a serum cholesterol of 614. Consequently, he was compared in Table II with the younger man who had an essential hyperlipemia with xanthoma tuberosum and previous myocardial infarction.

Duplicate samples of serum obtained before treatment were extracted in alcohol:ether as described by Bloor[16] and analyzed in duplicate for total lipids, total cholesterol and lipid phosphorus. Total lipids were determined gravimetrically, cholesterol colorimetrically by the Lieberman-Burchard reaction, and lipid phosphorus colorimetrically using a modification of the Fiske-Subbarow technic. A third 5 cc. sample was then brought to a density of 1.21 with NaCl and KBr as described by Lewis and Page[17] and centrifuged for thirteen hours at 30,000 r.p.m. in the 30.2 rotor of the Spinco Model L centrifuge. The top fraction was removed and diluted to 2 cc. with salt solution of 1.21 density and analyzed in the Spinco Model E ultracentrifuge, exposures being made at 0, 2, 10, 26 and 34 minutes after reaching a running speed of 52,640 r.p.m. In determining concentration, no effort was made to correct for the Ogston-Johnston effect.[18]

TABLE I

COMPARISON OF THE MEAN OF THE SERUM LIPID FRACTIONS AND ITS STANDARD ERROR IN HYPOTHYROID AND HYPERTHYROID PATIENTS

	Number of Patients	Serum Lipids (Chemical Analyses) (mg. per cent)					Serum Lipoproteins (Ultracentrifugal Analyses) (mg. per cent)			
		Total Cholesterol	Total Lipid	Phospholipid	Per cent Phospholipid	C/LP	$-S_{1.21}$ 0–10 (α-Lipoprotein)	$-S_{1.21}$ 20–40 (β-Lipoprotein)	$-S_{1.21}$ 40–70	$-S_{1.21}$ 100–400
Hyperthyroidism: Mean	25	176	627	194	31.45	22.68	142	137	47	31
± Standard error	..	7.7	26	6.24	0.84	0.58	10.2	12	4.33	5.38
Hypothyroidism: Mean	17	408	1404	370	27.88	27.25	174.5	350	143	83
± Standard error	..	25.4	117	20.9	1.04	0.99	15.3	32	23.2	22.3

RESULTS

Since it is well known that serum lipid values may be normal in hyperthyroidism and occasionally in hypothyroidism, it seemed advisable to compare the series of hyperthyroid sera with the hyperthyroid samples, as had been done by Mason, Hunt and Hurxthal,[1] in an effort to find the serum lipid fraction most influenced by thyroid activity. Table I presents the mean values of the chemical and ultracentrifugal fractions in these two groups. It can be seen that there is a highly significant difference ($P < 0.01$) between all of the various chemical fractions, the beta lipoprotein, and its faster-rising components, $-S_{1.21}$ 40–70 and less certainly ($P < 0.04$) 100–400. There is no significant difference ($P > 0.1$) in the alpha ($-S_{1.21}$ 0–10) lipoprotein. The chemical fractions present a twofold increase in the hypothyroid group, the alpha lipoprotein a 1.25-fold difference, the

faster rising beta lipoprotein fractions approximately a threefold rise.

The difference in alpha$_1$ lipoprotein concentration is not significant but the hyperthyroid group has a greater predominance of women, and particularly of younger women who might be expected to show a higher alpha$_1$ lipoprotein concentration. Hence, the lesser difference between the two groups in this fraction might be explained in part by these differences in age and sex. It has been well demonstrated that estrogen administration will increase the concentration of alpha$_1$ lipoprotein in the serum of either sex,[19,20] and that the alpha$_1$ lipoprotein concentration is lower in young men than in young women.[17]

The greatest difference appears to be in the concentrations of beta lipoprotein ($-S_{1.21}$ 20–40), and its faster-rising component, $-S_{1.21}$ 40–70 (equivalent to Gofman's S_f 12–20), which are much higher in hypothyroidism. It has been suggested that these lipoproteins correlate with atherosclerosis.[13] It is worthy of note, however, that ten patients with hyperthyroidism presented $-S_{1.21}$ 40–70 levels greater than 50 mg. per cent and seven had an $-S_{1.21}$ 100–400 greater than 40 mg. per cent. These patients included three with malignant exophthalmos, two with "essential" hypertension and one with the anginal syndrome and electrocardiographic evidence of arteriosclerotic heart disease. Thus it would appear that an overactive thyroid is not incompatible with an elevation of the faster rising material with flotation rates from $-S_{1.21}$ 40–100.

Mention has been made of a large concentration of alpha$_2$ lipoprotein in the serum of hypothyroid dogs[11] and, in an isolated instance, in one myxedema patient's serum.[21] In general there was no over-all or consistent increase of alpha$_2$ lipoprotein in these hypothyroid sera—although it was present in measurable concentration (>10 mg. per cent) in about one-third of the cases, a frequency comparable to the matched group to be presented. (Fig. 1B.) However one patient previously untreated and undiagnosed, who was severely myxedematous, presented a large alpha$_2$ peak distinct from the beta peak. (Fig. 1D.) The alpha$_2$ peak almost equalled the beta peak in amplitude and the pattern was obviously unique. The chemical findings in this case were also unique, there being a large neutral fat component; the cholesterol was unusually low, relative to the total lipid. The alpha$_1$ concentration was quite low. This pattern of a large alpha$_2$ lipoprotein and a low alpha$_1$ is seen in some cases of "essential" hyperlipemia, in certain nephropathies and in certain cases of biliary cirrhosis. The low C/P ratio and high neutral fat suggests the latter most strongly in this patient. In this regard our experience corresponds with that of Swahn.[9] One patient with hyperthyroidism and mild essential hypertension also had a large beta peak which migrated slowly enough to perhaps include an alpha$_2$ peak. (Fig. 1A.)

Comparison between the two matched groups in Table II reveals a tendency to higher serum lipid values in the hypothyroid subjects than in the patients with arteriosclerotic heart disease. None of the differences noted are statistically significant except for the beta lipoprotein ($-S_{1.21}$ 20–40). The differences in cholesterol-phospholipid ratio and $-S_{1.21}$ 40–70 are significant only at the $P < 0.10$ level of confidence, the former being higher in atherosclerotic patients, the latter in myxedema. By Fisher's t test, it could be shown that the beta lipoprotein level was significantly higher ($P < 0.05$) in the arteriosclerotic group than in myxedema, although the tendency in the other fractions was for the myxedema group to be higher. The probability that the difference might be due to chance became even less ($P < 0.01$) when the beta lipoprotein/total lipid or beta lipoprotein/alpha lipoprotein ratios were used.

COMMENTS

One myxedematous subject's serum, of seventeen such patients, did show a large amount of alpha$_2$ ($-S_{1.21}$ 20–25) lipoprotein previously described in hypothyroid dogs[11] and humans.[21] Except for this unique case, none of the other patients showed any significant increase in concentration of this lipoprotein fraction. We have confirmed the observation that hypothyroid dogs present a large alpha$_2$ fraction but, in fact, even normal dogs do not carry lipids with a beta globulin, but with the alpha globulins; hence the alpha$_2$ lipoprotein grows larger in induced canine hyperlipemia, e.g., diabetes. Also there is a wide variation in the flotation rate of the major (beta lipoprotein) peak from human to human, and sometimes in the same person. In some human sera we have seen an apparent reduction in rate of movement of the peak's nadir with increasing concentrations of the major component (Fig. 1C) and it becomes difficult

to separate this from the case in which the alpha$_2$ peak may be combined with the beta peak, defying resolution. (Fig. 1A.) This situation must be distinguished from an unquestioned second peak in the $-S_{1.21}$ range of 20–25 existing in the presence of a well defined beta lipoprotein peak at $-S_{1.21}$ 25 to 38. (Fig. 1D.) We have seen this consistently in three cases of hepatobiliary disease we have studied and in six patients with essential hyperlipemia, four of whom had suffered with symptoms (and had electrocardiographic evidence) of coronary artery disease. One of these patients apparently had a healed pyelonephritis.

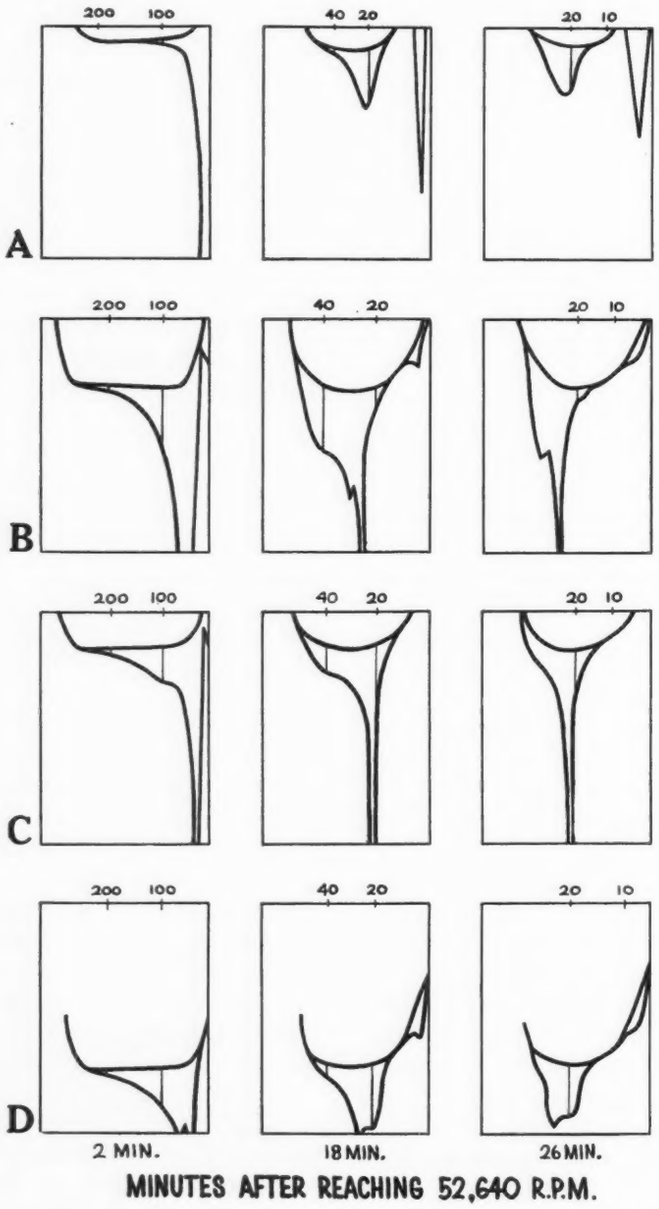

FIG. 1. Serum lipoprotein patterns in four patients. Flotation rate at density 1.21 and 26°C. A, fifty-six year old woman with essential hypertension and hyperthyroidism. (B.M.R. +71.) B, sixty-five year old female with myxedema and arteriosclerotic heart disease. (B.M.R. −30.) C, sixty-three year old female with myxedema. (B.M.R. −38.) D, fifty-seven year old man with myxedema, spondylolisthesis, right hip pain and inguinal hernias. (B.M.R. −36.)

TABLE II

COMPARISON OF HYPERLIPEMIC PATTERNS IN HYPOTHYROID PATIENTS WITH PATTERNS IN FAMILIAL HYPERCHOLESTEREMIA PATIENTS WITH CORONARY ARTERY DISEASE *

Patient		Sex and Age	Cholesterol (mg. %)	Total Lipid (mg. %)	Phospholipid (mg. %)	α Lipoprotein $-S_{1.21} < 10$ (mg. %)	β Lipoprotein $-S_{1.21}$ 20–40 (mg. %)	$-S_{1.21}$ 40–70 (mg. %)	$-S_{1.21}$ 100–400 (mg. %)	β Lipoprotein / α Lipoprotein Ratio	Per cent β Lipoprotein
Hypothyroidism	Coronary Disease										
Keu		F, 31	389	1098	328	246	230	209	322+	0.94	21.0
	Gre†	F, 25	337	963	320	295	365	63	30	1.24	38.0
Fai		F, 33	309	988	290	208	347	79	15	1.67	35.1
	Dav	F, 38	288	1020	303	208	598	67	110	2.87	58.6
Kam		F, 35	413	1485	360	155	475	213	55	3.07	32.0
	Lic‡	F, 27	480	1245	323	60	518	113	3	8.63	41.6
Sta		F, 44	654	2243	596	162	577	204	58+	3.56	25.7
	Keu	F, 60	646	2185	505	81	672	213	310	8.30	30.7
Gri		M, 48	540	1537	382	107	416	116	88+	3.89	27.1
	Cre	M, 25	571	1328	390	154	644	40	0	4.18	48.5
Hor		F, 50	412	1143	328	244	307	67	43+	1.26	26.8
	Hee	F, 52	393	1043	325	154	539	67	24	3.50	51.1
Tob		F, 50	362	1103	310	205	436	85	40	2.13	39.5
	Che	F, 50	371	987	301	132	307	38	0	2.32	31.2
Lew		M, 52	371	1090	302	188	374	106	3	1.99	34.3
	Ros	M, 51	355	1043	298	158	353	73	6	2.23	33.8
Fal		F, 56	421	1158	378	252	205	60	12	0.81	17.7
	Bak‡	F, 51	438	1328	365	161	769	146	18	4.77	58.0
Hal		M, 57	327	2520	472	93	180	234	255	1.94	07.2
	Ric	M, 53	340	1213	310	121	322	79	30+	2.66	26.5
Tob		M, 58	300	841	305	143	196	36	10	1.37	23.3
	Par	M, 55	313	1130	285	57	432	140	209	7.58	38.2
Cel		F, 60	400	1185	360	290	176	75	26	0.61	14.9
	Lou	F, 63	372	1140	367	380	599	128	9	1.58	52.5
Rig		M, 62	319	1290	298	67	390	140	52	5.32	30.2
	Ada	M, 60	311	913	255	107	295	103	48	2.76	32.3
Con		F, 63	410	1425	365	222	417	137	118	1.38	29.3
	Bab	F, 60	410	1058	338	228	392	104	16+	1.72	37.1
Kuc		F, 65	408	1875	480	108	611	394	106	5.66	32.6
	Car	F, 54	381	1050	308	100	410	115	52	4.10	39.0
Qua		M, 69	285	905	275	151	356	30	15	2.21	37.2
	Pax	M, 65	297	1008	300	165	304	55	24	1.81	30.1
Blu		M, 70	614	1990	463	129	289	249	193	2.24	14.5
	Bar	M, 44	534	2623	525	62	377	258	1010+	6.07	14.3
Mean:											
Hypothyroidism		53	408	1404	370	174.7	350.7	143	83	2.415	26.3
Coronary disease		49	402	1252	342	154.5	464.5	106	112	3.901	38.9
± Standard error:											
Hypothyroidism		..	25.8	118	20.9	15.5	32.0	23.2	22.3	0.373	2.2
Coronary disease		..	24.6	111	17.8	20.8	36.0	14.4	59.6	0.581	2.8

* Patients matched as to sex, age and serum cholesterol level.
† Family history only of coronary disease.
‡ Xanthoma tuberosum without proved coronary disease.

The one patient with myxedema who presented a definite double peak of the major lipoprotein present, the slower peak of the two falling in the centrifugal range of alpha$_2$ lipoprotein (Fig. 1D), had none of the aforementioned complications clinically but did suffer from arthritis of obscure etiology which involved the back and right hip. One of the hyperthyroid patients who had essential hypertension presented a large slow moving peak (Fig. 1A), the nadir of which occurred at $-S_{1.21}$ 23 and could be interpreted as a combination of alpha$_2$ and beta lipoproteins which could not be resolved. The alpha$_1$ lipoprotein is apparently little affected by thyroid activity although our data are not designed to test this conclusively.

In all situations in which hyperlipemia or hypercholesteremia exist, the tendency is for other fractions, both chemical and ultracentrifugal, to rise concurrently. This tendency can be seen in either coronary atherosclerosis or myxedema, yet the ultracentrifugal studies offer finer differentiation. While it may be said that the hypercholesteremia of both groups is associated with an increase in serum beta lipoprotein, and we would agree with Malmros and Swahn[10] that the lipid pattern is similar in hypothyroidism and atherosclerosis, yet it may be further noted that the beta lipoprotein level is proportionately much higher in atherosclerosis for a given degree of hypercholesteremia. This lends further support to the observations of Pratt,[22] Eder, Russ and Barr[23] and the conception of Page[24] who suggested that the primary abnormality of the serum lipids in coronary atherosclerosis may be an excessive beta lipoproteinemia, either relative to the level of alpha lipoprotein or absolutely. Gofman's fraction, our $-S_{1.21}$ 40–70, seems to mirror the beta lipoprotein in general and should probably be considered a portion of that moiety. This, coupled with the fact that certain hyperthyroid patients still manage to have abnormal levels of $-S_{1.21}$ 40–400, suggests that the mechanism of development of the serum lipid abnormality differs in atherosclerosis from the hypercholesterolemia of myxedema.[25] However, if the "intimal infiltration" theory of atherogenesis is correct, and a particular lipid fraction of the serum is more culpable than others in atherosclerosis, any lipoprotein or chemical lipid fraction found associated with atherosclerosis can also be found, and in high concentrations, in myxedema. In other words this difference is only relative, not absolute, and in no way helps to settle the controversy as to the atherogenicity of the hypothyroid state.

SUMMARY

Serum lipids and serum lipoproteins were studied in twenty-five hyperthyroid and seventeen myxedema patients. Mean total lipid, total cholesterol and phospholipid levels were all significantly higher in the latter group. The beta lipoprotein and faster rising lipoprotein moieties showed a particularly striking increment, and contrasted with an insignificant difference in the alpha lipoproteins.

The increase of the serum lipids in patients with hypothyroidism is qualitatively indistinguishable from that seen in idiopathic hypercholesterolemia which is so often associated with coronary atherosclerosis. However, when such hypercholesteremic patients are matched with hypothyroid patients as to sex, age and cholesterol level, a significantly higher beta lipoprotein fraction is found in the former group. This suggests that the hyperlipemia of atherosclerosis arises through a mechanism which is different from that of myxedema. This observation is also consistent with the idea that the primary abnormality of the serum lipids in atherosclerosis is an elevation in the level of beta lipoprotein.

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The Night-eating Syndrome*

A Pattern of Food Intake among Certain Obese Patients

ALBERT J. STUNKARD, M.D., WILLIAM J. GRACE, M.D. *and* HAROLD G. WOLFF, M.D.
New York, New York

NONE of the numerous recent studies of obesity has dealt with the eating patterns of obese patients in more than a cursory manner. The rare papers on the subject have reported that obese patients eat more frequently than the non-obese,[1] less frequently,[2] or even that decreased activity rather than a change in eating habits leads to obesity.[3] In two papers incidental mention has been made that obese patients eat more at night.[4,5]

Observation of twenty-five obese patients at a special study clinic of the New York Hospital has disclosed that the eating patterns of a large number form a distinctive syndrome characterized by nocturnal hyperphagia, insomnia and morning anorexia. Such a pattern was not found in any of thirty-eight subjects without history of weight disorder. This "night-eating syndrome" was particularly prominent during periods of weight gain and life stress. An effective reducing regimen was not possible in its presence, and it appeared to be intimately related to the pathogenesis of obesity.

METHOD

The subjects of this report were seen in a special study clinic of the New York Hospital where they had been sent from other departments because of the severity of their obesity or difficulty in its management. The group thus includes a high proportion of emotionally disturbed individuals, but whether this proportion is higher than in any group of comparably severe obese patients is conjectural.

The report includes all obese patients referred to the clinic who were seen at least four times. It should be noted that only two patients failed to keep at least four appointments, so that the series comprises 93 per cent of the patients initially referred, including the only two men. The reason for the great preponderance of women is not clear.

The median age of the patients was thirty-five years (range eighteen to fifty-six). Percentage of overweight was determined from the tables of the Medico-Actuarial Mortality Investigation of 1912[6] which used clothed subjects in shoes. Following Keys,[7] the current study used these standards for lightly clothed, barefoot individuals without correction for either height of shoes or weight of clothes. The resulting average value of 68 per cent overweight (range 22 to 137) is thus lower than would be calculated from standards of "ideal" weight.

The study of each patient included a detailed history and physical examination, together with routine laboratory tests and any indicated special procedures. Most of the patients were seen for an hour every week or two over a period of six months. Three had only four interviews, and two (H. G. and M. B.) had more than 100. Medication was prescribed when indicated but the focus of the treatment was supportive psychotherapy combined with environmental manipulation. In a few of the patients more intensive psychotherapy was attempted. (Table I.)

Data about the patient's diets were obtained from three sources: the patient's record of food intake, the routine dietary history in the nutrition clinic, and a careful study of eating habits during the treatment period. The intake was often recorded as much as 400 calories per day higher by the second method, and 800 calories higher by the third. Such an increase in the caloric intake reported by obese patients when subjected to more detailed inquiry agrees well with published reports[8] and attests to the accuracy of the information obtained during the treatment periods. Reducing diets were prescribed only on the patient's request and the

* From the Departments of Medicine and Psychiatry, New York Hospital-Cornell Medical Center, New York, N. Y. This work was supported in part by the Research and Development Division, Office of The Surgeon General, Department of the Army. Supported in part by a grant from the Commonwealth Fund.

physician attempted to place the patient under no obligation to adhere to the diet. These were usually standard diets of 1,200 calories, containing 70 gm. of protein, 45 gm. of fat and 130 gm. of carbohydrate.

amounts of food during the evening and night and no one was considered to manifest the syndrome unless he ate at least a quarter of his total calories for the day during the period following the evening meal. Thus a significant part

TABLE 1

No.	Patient*	Age	Height	Weight (lb.)	Over-weight (%)	Components of Syndrome Present	Weight Loss in Clinic	Previous Maximal Weight Loss	Complications
1	D. M.	23	5′ 0″	275	137	2 (sometimes alcohol instead of food)	0	70 lb.†	0
2	H. G.	44	4′ 10½″	290	130	3	0	80, 150 lb. (in hospital)†	See case report
3	L. M.	30	5′2″	260	110	2 (no insomnia)	0	50 lb.	"Neurasthenia"
4	M. B.	18	5′ 0″	230	105	3	30 lb.	0	0
5	E. S.	30	5′ 6½″	280	100	3	30 lb. (in hospital)	30 lb.	0
6	M. L.	25	5′ 5″	255	95	3	0	60 lb.†	"Neurasthenia"
7	S. B.	36	5′ 7½″	283	90	0	45 lb.†	50, 45 lb.†	0
8	F. W.	48	5′ 5½″	290	86	0	45 lb.†	80 lb.†	0
9	E. M.	36	5 2½″	238	84	3	0	50 lb.†	Psychotic depression
10	A. R.	28	5′ 4″	235	81	2 (no insomnia)	10 lb.	50 lb.†	Severe anxiety
11	E. H.	35	5′ 3″	235	81	0	0	0	0
12	L. S.	27	5′ 2½″	220	77	3	12 lb.	18 lb.	"Neurasthenia" previously, asthma and bleeding ulcer in clinic
13	A. F.	56	5′ 3½″	245	71	0	105 lb.†	0	0
14	S. V.	31	5′ ½″	198	62	3	0	0	0
15	M. A.	42	5′ 1″	200	54	3	0	0	0
16	O. A.	38	5′ 11″	262	51	3	20 lb.	45 lb.†	0
17	S. M.	51	5′ 2½″	204	46	3	0	0	0
18	L. C.	30	4′ 9½″	166	43	0	50 lb.†	75, 45 lb.†	0
19	M. C.	49	5′ 0″	183	39	3	40 lb.†	0	Psychotic depression
20	S. G.	34	5′ 3″	176	35	3	0	70, 45 lb.†	Depression (2×)
21	I. G.	50	5 1″	180	33	3	0	0	0
22	M. P.	26	5′ 5″	175	32	3	20 lb.†	0	0
23	R. G.	18	5′ 2″	148	26	3	0	0	0
24	S. S.	43	5′ 2½″	166	22	2 (sometimes alcohol instead of food)	0	28 lb.†	"Neurasthenia"
25	B. .S	54	5′ 5″	180	22	3	0	14 lb.	0

* All patients were women with the exception of No. 8 and No. 16.
† At least one-third of excess weight.

RESULTS

Definition of Syndrome. An effort was made to establish gross criteria for the three major findings which comprise the night-eating syndrome and which might serve to distinguish it from other patterns of eating. First, and of greatest importance, is the consumption of large

of the total caloric intake, and a major part of the excess intake, occurs during a time when the food intake of non-obese people is negligible. The second criterion is sleeplessness, at least until midnight more than half of the time, and the third is morning anorexia with negligible food intake at breakfast. In no case did this

include more than a cup of coffee and a small glass of orange juice.

Specificity of Syndrome. The eating pattern of the obese group was compared with that of thirty-eight subjects who had no past history of weight disorder. This latter group was composed of graduate and student nurses routinely examined in the personnel health clinic of the medical center. All of the subjects were women and the median of their ages was twenty-four years, ranging from twenty-one to forty. The majority were residents in the nurses' home where they were able to obtain meals when they were off duty. In addition, permission to keep food in their rooms and a refrigerator on each floor allowed food intake to be largely independent of the regular cafeteria hours. Further evidence that the findings in the control group were not due to inaccessibility of food is provided by the rather high incidence of obesity in the nurses' home.

Of the thirty-eight control subjects, not one reported the night-eating syndrome. In considering the components of the syndrome, most of the group gave a history of food intake following the evening meal, commonly a sandwich and glass of milk before going to bed, but in no case did this approach 25 per cent of the daily food intake. One of the group reported insomnia. Nine reported that they had little or no appetite for breakfast but three of these said that they ate a substantial breakfast anyway.

Incidence of Syndrome. The night-eating syndrome in its entirety was reported by sixteen of twenty-five patients, and it was present with minor variations in another four patients. Of these latter four, two patients often consumed alcohol instead of food during the evening while two others did not report insomnia despite a large caloric intake following the evening meal.

Although these twenty patients reported that the night-eating syndrome occurred much of the time, it was not invariably present. Accordingly, an attempt was made to determine in what circumstances it was most likely to occur. Most of the patients agreed that they ate at night during two closely related situations—periods of weight gain and periods of life stress.

All twenty of the patients who reported night eating said that it was the major pattern during periods of weight gain. Two of the remaining five patients (S. B. and L. C.) said that during their periods of weight gain they ate increased amounts at mealtimes, one (F. W.) drank large amounts of alcohol without restricting food intake, one (A. F.) ate indiscriminately throughout the day and one (E. H.) maintained her usual food intake while at bedrest for treatment of pulmonary tuberculosis. Eighteen of the twenty patients exhibiting the night-eating syndrome said that it was most conspicuous during periods of life stress. Both of the patients (B. S. and L. M.) who did not make this correlation were denying obvious emotional disturbances while acknowledging presence of the syndrome.

Night-eating Syndrome and Prognosis. Presence of the night-eating syndrome influenced (1) results of weight reduction programs and (2) the incidence of untoward reactions to such programs.

1. Results of weight reduction programs: Loss of one-third of patient's excess weight was selected as indicating modest success of a weight reduction program. By these standards only six of the twenty-five patients reduced successfully. Such results are poorer than those in other series,[9–13] a circumstance perhaps arising from the selection of a large number of patients who had already proved difficult to manage. The high incidence of the night-eating syndrome in this group may reflect this same selection, for there is a striking correlation between presence of the syndrome and failure of dietary regimens. Thus of the twenty patients reporting the syndrome, only two were able to lose more than one-third of their initial excess weight. In one of these (M. C.) the weight loss occurred in the course of a psychotic depressive reaction; in the other (M. P.) it totaled only twenty pounds in a woman who was initially one of the least overweight. In contrast, of the five patients who did not report the pattern, four (M. B., E. S., A. R. and O. A.) lost an average of sixty-one pounds, or 67 per cent of their excess weight.

Five patients manifesting the night-eating syndrome lost from ten to thirty pounds without being able to maintain a reducing regimen. Their experience throws light on the significance of night eating as an index of refractoriness to weight reduction programs. Thus it was during temporary remissions in the syndrome that this weight loss occurred in four of these five patients.

The patients' past histories of attempts at weight reduction were similar to the findings during treatment in the clinic. Of the twenty patients exhibiting the syndrome, only eleven

had ever succeeded in losing more than one-third of their excess weight. On the other hand, of the five patients not reporting the syndrome, four had carried out successful weight reduction programs in the past.

2. Untoward reactions to weight reduction programs: Untoward reactions to weight reduction in obese patients have recently been given prominence, largely through the publications of Bruch.[14,15] The prevalence of such responses is emphasized by the experience of the patients in the present series, who suffered a total of ten severe complications during previous and current efforts at weight reduction.

Considering first the results of treatment of night-eating patients in this clinic, one (M. C.), as already noted, suffered a psychotic depressive reaction two months after she began to diet. Another (L. S.), who had lost 12 pounds in the first month of a reducing regimen, was forced to stop dieting by the onset of severe bronchial asthma and bleeding peptic ulcer. There were no untoward reactions among the five patients not showing the syndrome.

Dramatic evidence of the influence of the night-eating syndrome on the incidence of untoward reactions to dieting is obtained from the history of the patients' past experience with reducing regimens. As has been noted, only eleven of twenty patients with the night-eating syndrome had previously been able to lose more than one-third of their excess weight. In eight of these eleven instances this weight loss was accompanied by disabling emotional illness. Four of the patients presented a remarkably similar picture of neurasthenic type characterized by feelings of futility, depression of mood and inordinate fatigue leading to confinement in bed for as long as four months. Three patients stopped weight-reducing regimens because of depressive reactions, and one following the onset of severe anxiety. Therefore, of eleven patients with a past history of significant weight loss, only three achieved this without disabling complications. One of these three patients (H. G.), reported subsequently, experienced severe anxiety in the course of a reducing regimen but factors other than diet seemed primarily responsible.

In contrast to this startling incidence of disability during attempts at weight reduction among patients with the night-eating syndrome is the infrequency of such complications in the group not showing the pattern. Although this latter group contained only five patients, four had previously lost significant amounts of weight without complication.

CASE REPORTS

The following two case reports illustrate various aspects of the night-eating syndrome. In the first, prolonged dietary restriction leading to a marked weight loss did not abolish the syndrome or prevent its intensification in a situation of life stress.

CASE 1. H. G. was a forty-three year old single woman clerical worker who was observed over a two-year period in another hospital to which she had been admitted for treatment of cardiac failure on the basis of hypertensive disease and massive obesity.

The patient was the eldest of four children born to an orthodox Jewish family in a small midwestern city. Her father, a quiet, bookish man took little part in the family life; her mother, on the other hand, "ran everything."

Childhood and adolescence were characterized by vacillating and inconsistent parental care, and intense, unsuccessful rivalry with a younger brother. At the age of twenty-one the patient suffered severe lacerations in an automobile accident, to which her mother reacted with great distress. Soon thereafter the mother developed incapacitating cardiac symptoms which she blamed on worry over the patient, and for the next nine years she remained a semi-invalid. During this time she induced the patient to devote herself wholly to her care and to abandon her hopes for independence, a career and marriage. Some months after her mother's death the patient, then thirty-one, learned that the doctor had considered her mother's long-standing condition a neurosis, and her symptoms largely exhibitionistic and exploitative. The patient felt betrayed and bewildered, and left home to come to New York.

During the ensuing seven years she gained weight from 200 to 400 pounds (height 4 feet 10½ inches) by overeating in a pronounced night-eating pattern. Thus she rarely ate before noon, and at supper began her large intake of sweet foods which continued until she went to bed late at night. During these hours she was assailed by loneliness and anxiety. To lessen the distress she kept someone with her as much as possible and, when she was alone, left the door and windows open, all the lights burning and played the radio loudly. She rarely fell asleep

before midnight and usually woke within an hour, anxious and hungry. At such times she would eat a pint of ice cream, drink a bottle of Pepsi Cola and, temporarily sated, fall asleep for another hour before the cycle was repeated. She awoke three or four times a night in this manner.

By the age of thirty-five the patient's obesity and hypertension had so disabled her that she sought medical attention, and for a period of six years she received general medical and psychiatric care as an outpatient. Ultimately cardiac failure became so severe that hospitalization was necessary. This only partially decreased the nocturnal anxiety and hunger but rigid caloric restriction succeeded in effecting a loss of 150 pounds over a period of one year. At this time two traumatic events occurred: a physician to whom the patient had become much attached left the hospital, and the patient underwent an operation for umbilical hernia which was complicated by wound infection. She reacted with intense anxiety and petulant, infantile behavior. These were most marked at night when she would spend as much as four hours tearfully pacing the corridors with intermittent futile attempts at reading and knitting. As a therapeutic trial, free access to food was permitted and the patient immediately returned to the night-eating pattern. This was associated with a weight gain of 50 pounds in the course of the next two months and no apparent improvement in her emotional disorder.

In the following patient remission and exacerbation of the night-eating syndrome followed promptly upon changes in her life situation, and were associated with marked variation in the success of a dietary regimen.

Case II. E. S. was a twenty-nine year old housewife of Irish ancestry who was treated in a special study clinic of the New York Hospital over a period of one year. She came for treatment of her obesity as a result of urgent medical advice following recurrent severe attacks of thrombophlebitis.

The patient was the eighth of ten living children of a mother who had had ten additional pregnancies. Her restrictive and arbitrary father worked as a truck driver but the income from his sporadic employment never permitted the family more than a marginal existence. The patient remembered her childhood as a time of hardship and deprivation, and of great bitterness toward a mother who, she felt, exploited her. At the age of eighteen she married the neighborhood alcoholic in an effort to escape this home environment and soon found herself in an even more unpleasant situation. During the next eight years she gained 100 pounds, attaining a weight of 280 pounds (height 5 feet, 6 inches), which she maintained during the three years before admission to the clinic.

The patient's manner was pleasant and friendly during the treatment periods but she did not participate actively, and her communications had a curiously impersonal quality. She was usually late to appointments and attendance was irregular.

Her pattern of food intake was characteristic of the night-eating syndrome. During periods of emotional turmoil, in which the patient was either gaining weight or trying unsuccessfully to lose it, she awoke in the morning completely anorexic and ate no breakfast and little lunch. Supper, which she ate in the early evening, was large, yet provided only transient satiety. During the rest of the evening, and often until early morning, she nibbled at various foods distinguished mainly by their sweetness. The patient was unclear about the specific incentive to eating at these times but suggested that it was due to the anxiety she felt at night. This was most severe when she was alone, and was often experienced as a fear of someone breaking into the house to harm her. None of the measures she took provided more than partial relief; these included, besides eating, having company in the house and, when she had to be alone, keeping the radio and lights on. The presence of her husband sometimes reassured her but often quarrels with him had precipitated her anxiety and at such times he served only to upset her further. Insomnia and eating continued until at least midnight, often until two or three in the morning, and throughout the treatment period she rarely slept more than four hours.

After the patient had been receiving treatment for seven months a recurrence of phlebitis developed which made it necessary for her to enter the hospital. She greeted this development with relief and gladly laid down her domestic responsibilities. Within a day there was a striking change in the eating pattern. The morning after admission the patient awoke with a desire to eat breakfast for the first time in months, went on to consume a small lunch and supper, and had no desire to eat during the

evening or night. This was more remarkable in that the pain in her legs kept her awake much of the night during the first week of hospitalization. Thereafter she slept well and at no time complained of hunger. She adhered without difficulty to an 800 calorie diet and lost twenty-eight pounds in thirty-one days.

This marked change in eating pattern was paralleled by a great decrease in free anxiety and, despite her pain, the patient seemed more at ease than at any time during the previous months as an outpatient. She attributed this change in both comfort and eating pattern partly to the experience of hospitalization and partly to the presence of a roommate. "Mrs. C. keeps me feeling good in the evenings by talking to me so I don't feel like eating."

The patient made every effort to remain in the hospital; and when she finally returned home, it was with greatest reluctance. Within twenty-four hours the night-eating syndrome recurred. The morning after her arrival home she awoke anorexic, did not begin to eat until evening and stayed up until 3:00 A.M. nibbling. Her husband, who had stopped drinking while she was in the hospital, began again soon after her return, and relations between them which had improved during her hospitalization deteriorated rapidly. During the first month following her discharge the patient gained weight at a rate of 2 pounds a week.

COMMENTS

In recent years there has been a growing appreciation of the emotional disturbance in many overweight people and even of the fact that their excess weight has been gained in relatively short periods of positive caloric balance. In point of fact, a large number of obese patients are losing weight much of the time and it is short periods of rapid weight gain which undo the results of weeks and months of dieting. If obesity be considered a scar of preceding periods of positive energy balance, it is just these periods which are of significance in its pathogenesis. Yet the conditions existing during these crucial times are largely obscure, as can be judged from the fact that the night-eating syndrome described here has not been reported previously. This is the more remarkable in that it is well known to the obese patients themselves, as well as to those relatives, nurses and dietitians who have much contact with them.

The major significance of the night-eating syndrome may lie in its relation to the life situation of the individual who manifests it. Although it is not present all of the time, even in the very obese, occurrence of the syndrome can be predicted during periods of weight gain and life stress, and these three variables are linked with remarkable consistency. What, then, is their interrelationship?

The relation between the eating pattern and life stress appears clear. They regularly occur together, and although the obese patients may respond to stress in other ways as well, when the night-eating syndrome is found, it is in situations of life stress.

The relation of these two factors to the periods of weight gain is less immediately apparent. Although it is difficult to conceive of life stress as being a consequence of weight gain, night eating could be. The experience of the two cases cited, however, argues against this. Thus the first patient (H. G.) manifested the night-eating syndrome at intervals over a year's time despite forcible restriction of food intake resulting in a weight loss of 150 pounds. In the second patient (E. S.) the syndrome disappeared within a day and reappeared as promptly following changes in her life situation, hardly long enough for changes in weight to have had an effect. It therefore seems justified to conclude that the night-eating syndrome is not a result of weight gain, overeating or any metabolic consequence of these. The syndrome appears rather to represent a response to stress of a type peculiar to certain obese patients, and one intimately related to the overeating which leads to their obesity.

Alterations in diurnal rhythms in response to stress are known to the clinician but they are not common. Two which have received some prominence are the sleep reversal following encephalitis and the "morning-evening variation" of the depressive reaction. The night-eating syndrome appears distinct from these two. None of the patients in this series had a history compatible with encephalitis. And while their food intake increases during the day, as that of depressed patients, their distress also increases, in contrast to the experience of patients with depression.

That the normal diurnal eating pattern may be important in the maintenance of caloric balance is suggested by an observation of Brooks.[16] This author has noted that destruction of the ventromedial nuclei of the hypothalamus

abolished the normal pattern of nocturnal eating in the rat. During the subsequent period of weight gain in the so-called hypothalamic obese rat the normal pattern is replaced by chaotic eating throughout the twenty-four hours.

Significance of Syndrome for Weight Reduction. It has long been recognized that there are many patients who cannot maintain a reducing diet long enough to make it worth either their effort or the doctor's time. However, it has only recently been pointed out by Bruch that in addition to these patients who cannot lose weight there is a group of emotionally disturbed obese patients who should not even try. There is too great a danger that such efforts, "if rigidly enforced . . . may precipitate serious mental disturbance."

There are unfortunately no criteria to select those patients who might undertake dieting with safety and reasonable hope of success. If the results of this study are confirmed in a series including a larger number of obese patients not manifesting the night-eating syndrome, recognition of the syndrome could be of value in deciding whether to restrict food intake. The presence of the syndrome in an obese person indicates that it will be very difficult for him to lose weight, and that he may attempt it only at a risk far outweighing the benefits to be derived. However, the fact that the syndrome is not always present, even in those persons who may exhibit it much of the time, suggests that dieting may not be permanently contraindicated for such individuals. On the contrary, the sensitivity with which it reflects the emotional state of the patient might allow the syndrome to serve as an index of the success of psychotherapeutic measures. Thus remissions could be taken as indication that weight reduction might reasonably be attempted. Finally, reducing diets can be prescribed with confidence for those patients who have never manifested the syndrome.

Dexedrine®. The most widely prescribed drug in the treatment of obesity is probably dexedrine, a circumstance dependent upon its well recognized action in depressing appetite. Reports of its value in actual practice have, however, varied widely.[5,17] Demonstration of a night-eating syndrome in many obese patients may help to reconcile these conflicting findings as well as provide a better rationale for use of the drug in weight reduction programs. If the patient does a major part of his eating at night, in conjunction with anxiety and insomnia, a drug which promotes sleeplessness is of doubtful value and its use during the period of morning anorexia is little more than a gesture. On the other hand, when the patient's overeating occurs during the daylight hours, the maximum appetite-depressing effect of dexedrine is obtained without the undesirable side effects.

Estimation of Caloric Intake. A common and well recognized characteristic of obese patients is their tendency to underestimate their caloric intake. Although this can be explained easily enough on the basis of the shame involved in acknowledging how much they have eaten, recognition of a night-eating syndrome may throw further light on the problem. Beaudoin[8] has shown that underestimation of caloric intake by obese subjects is greatest in regard to food eaten during the latter part of the day. She adduced no reason for this finding but Bruch's investigation of certain obese patients has revealed a marked repression of the knowledge of food eaten at night.[18] This is associated with early feeding problems, eating as defiance, and the later unconscious rationalization that "food eaten after dark does not count." Some such selective inattention renders more understandable reports of food intake in the 1,200 calorie range by patients who continue to gain weight. This is perhaps all they do eat during the daylight hours.

Relation to Research Procedures. Presence of the eating pattern described here has certain implications for research in obesity. Thus investigations made during the morning and early afternoon hours may give information about the patient which is quite different from that which would be found by investigation during the evening and night hours when he is overeating.

Tumor of the Pancreas. Since the concept of endogenous obesity has fallen into disrepute, the differential diagnosis of obesity has involved few considerations of structural disease. One notable exception has been the obesity associated with insulin-secreting tumor of the pancreas. In this condition hunger and maximum food intake classically follow periods of food deprivation, most notably during the morning hours either before breakfast, or in its absence. Recognition of the night-eating syndrome, with its morning anorexia, therefore, is helpful in excluding the possibility of organic hyperinsulinism.

Etiology. The etiology of the night-eating syndrome has not been determined. Furthermore, its characteristics do not reveal whether the

mechanisms involved in its pathogenesis are primarily physiologic or psychologic. Thus disordered carbohydrate metabolism involving increased tolerance to glucose has been reported in certain cases of obesity.[19,20] If, as seems likely, utilization of carbohydrate is under the control of hormones which are in part regulated by the intake of carbohydrate, there must be a mechanism which inactivates or decreases the secretion of these hormones with a failing carbohydrate supply. Such a sequence would involve the formal properties of a servomechanism as described by Wiener,[21] and in normal function would involve utilization of negative feedback to maintain the system in equilibrium. Disturbance in the feedback mechanism could lead to breakdown of the system in such a way that recurrent bouts of hypoglycemia would succeed each other in accelerating succession. Such changes might find expression in the periods of decreasing satiety noted during the evening. When sleep finally interrupted the intake of carbohydrate, the reactive hypoglycemia would cease, and the blood sugar would remain stable throughout the morning period characterized by anorexia.

Another explanation of the night-eating syndrome is suggested by the observation that the evening anxiety and impulse to eat often can be interrupted by the most simple interpersonal means. Talking with the physician at midnight may be as useful as massive sedation in temporarily alleviating both the anxiety and the need to eat. The period of going to bed, the evening, is traditionally associated in children with the greatest anxiety, presumably due to the fear of separation from the parent and the threat of the breakthrough of anxiety-productive conflict, as in dreams and nightmares. The obese women, in this group at least, were for the most part remarkably immature characters who relied inordinately on praise and tokens of love for the control of anxiety and the regulation of self-esteem. It seems possible that, as in children, the breakthrough of anxiety during the evening may result from this same interruption of their source of affection and approval. It is unlikely that the night-eating pattern is more directly related to a childhood one, as none of the patients could definitely remember such an eating pattern in childhood, nor had this period been characterized by a greater incidence of night terrors or bedtime conflict than would be expected in any comparable group.

SUMMARY AND CONCLUSIONS

1. A distinctive eating pattern of obese patients is described. This "night-eating syndrome" is characterized by nocturnal hyperphagia, insomnia and morning anorexia.

2. The syndrome was present in twenty of twenty-five obese patients treated in a special study clinic and in none of thirty-eight non-obese subjects.

3. Patients manifesting the syndrome had great difficulty losing weight and experienced a high incidence of complications in their attempts.

4. It is suggested that the syndrome represents a response to stress of a type peculiar to certain obese patients, and that it is intimately related to the pathogenesis of their obesity.

Addendum: A description of morning anorexia and evening hyperphagia in obese patients recently appeared in a paper entitled "Treatment of Obesity with a Low Protein, Calorically Unrestricted Diet," by V. P. Dole, I. L. Schwartz, J. H. Thaysen, N. A. Thorn and L. Silver, *Am. J. Clinical Nutrition*, 2: 381, 1953.

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Review

The Metal Chelate Compounds of Urine*

Their Relation to the Initiation and Growth of Calculi

WILLIAM H. BOYCE, M.D., FRED K. GARVEY, M.D. *and* CHARLES M. NORFLEET, JR., M.D.
Winston-Salem, North Carolina

URINARY calculi are composed of an organic matrix and a crystalline body. This matrix may be an inert inclusion present by chance association with the growing stone, or may possibly serve in a purely physical role as an adhesive binder to hold the crystals in an organized structure.[13] That it may utilize chemical bonds to play a more active role in the formation and growth of calculi is suggested by the recent investigations of Howard[14] and Engel.[10,11]

No scientific approach to the prevention of urinary calculi seems possible until this question of the chemical activity or inertness of the organic matrix has been answered. It is the purpose of this report to correlate some of the biochemical and physicochemical properties of the matrix with those of the crystalline components of urinary calculi.

CRYSTALLINE COMPONENTS OF CALCULI

Table 1 summarizes the findings in 500 consecutive analyses of urinary calculi at the Bowman Gray School of Medicine. Stones which contain as much as 95 per cent by weight of a single crystalline structure are listed as "pure." The limitations of the qualitative chemical methods for analysis of stones have been clearly demonstrated by Prien and Frondel.[21] The crystallographic studies of these authors have added much to our knowledge of the crystalline components of urinary calculi but the internal structure and mechanisms of growth of the crystal lattice require further study. Many crystalline structures have empirical formulas which do not exist as molecular units in any other state. A single atom or ion is sometimes included in the formation of a crystal for no apparent reason other than to complete the particular crystal lattice. The mechanisms by which either adsorbed ions or units of structure are exchanged between the surface of crystals and the surrounding solution remain a controversial subject.[15] The bonds which maintain these units of the crystal lattice in their spatial relationships are so arranged that almost any large crystal, such as sodium chloride[8,17] or hydroxyapatite,[22] is in reality a single molecule.

TABLE 1
CHEMICAL COMPOSITION OF 500 RENAL AND URETERAL CALCULI

Primary Constituents	Per cent Total
Pure—95% by weight:	
Calcium phosphate	36.6
Calcium oxalate	11.2
Uric acid	3.4
Cystine	0.4
Mixed:	
Calcium phosphate and oxalate	44.2
Uric acid with phosphate and/or oxalate	4.2
	100.0

Secondary Constituents (not included above): Magnesium ammonium phosphate present in 12 per cent; traces of uric acid present in 8 per cent; only 6 per cent of calcium phosphate stones were free of other constituents.

The general rules relative to crystal formation and growth[8] have a limited applicability to the study of urinary concretions. Crystallization may be facilitated by nuclei which present sur-

* From the Department of Urology, Division of Surgery, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C. This investigation was supported by a research grant from the National Institute of Arthritis and Metabolic Diseases, of the National Institutes of Health, Public Health Service.

faces favorable to deposition of the solid phase. The component ions and atoms of a given crystalline substance tend to "fit" into the lattice structure on the surface of like crystals. Thus crystalline uric acid nuclei tend to grow by the addition of uric acid crystals. A basic unit of hydroxyapatite crystal[22] grows by additions of the exact quantities of calcium, phosphate and hydroxyl ions necessary to duplicate its crystal lattice. There is a preferential formation of large concretions, since a small mass is attracted to larger masses having relatively less surface area and consequently less total surface energy.

The fact that certain materials are available for crystallization in biologic solutions does not necessarily mean that they are insoluble, hence availability and solubility are not synonymous in this respect. However, both the availability for crystallization and the solubility of a given ion, atom or compound are influenced by a variety of forces. These include the hydrogen ion concentration, the buffer systems, the total ionic concentration, the relative electrical charges, the zeta potential, the adsorption of relatively insoluble units by highly soluble molecules and the formation of soluble and insoluble coordination or chelate compounds. For example, calcium in a solution of orthophosphates has entirely different properties from those which it possesses in a solution of condensed phosphates. It should be borne in mind, however, that the rules of physical chemistry are devised under carefully defined laboratory conditions, and that the application of one or two of these rules "out of context" to complicated biologic systems is usually impossible.

Solute Phase of Crystalline Components of Calculi. Urine is a buffered, ionic and molecular solution. It contains organic suspensoids of molecular weights up to seven million,[25] and inorganic units as small as the hydrogen ion. There is no rationale for comparing the solubility of these materials in water to their solubility in urine. Only confusion can result from such statements as "The urine is normally twenty times saturated with respect to calcium oxalate."[16] Urine is not normally supersaturated with respect to calcium ions, since a neutral salt of calcium can be titrated into a twenty-four-hour specimen of urine to double the average content of calcium without precipitation.[3] This same observation applies also to the oxalic acid radical.

Hypercalcinuria is not essential to the development of calculi.[7] The majority of our patients with renal calculi, but without evidence of such associated syndromes as multiple myeloma, hyperparathyroidism or renal disease, do not have an increase in the twenty-four-hour excretion of urinary calcium. Neither do the majority of patients with acidosis,[1] multiple myeloma, hyperparathyroidism[19] or thyrotoxicosis[2] have urinary calculi, even though increased excretion of urinary calcium is a consistent finding in these and other disease states.[1] Although the incidence of urinary calculi is much greater in such patients than in the population as a whole, it is apparent that hypercalcinuria *per se* is not the sole etiologic factor.

An increase in the quantity of soluble macromolecules or "protective colloids" in the urine cannot explain the absence of calculus formation in the majority of patients with hypercalcinuria. Removal of these colloids by ultrafiltration does not significantly influence the precipitation of the urinary salts.[3] Furthermore, the total quantity of colloids present in the urine of patients with calculous disease is much greater than in normal urine.[4] Some of these biocolloids are present in urine as a result of glomerular filtration while others are products of epithelial secretion. In general, the former are the proteins present in serum, and they carry into the urine with them their normal complement of bound calcium. Since the urinary pH is usually much lower than that of the plasma, these proteins will bind even less calcium in urine than in plasma. The urinary colloids derived from the epithelial secretions are largely composed of "uromucoid,"[5] which has a molecular weight of seven million.[25] The quantity of this component is much increased in the urine of all patients with calculous disease, and it is completely insoluble in urine of average concentration. There is thus no basis for the assumption that, because some colloidal solutions increase the solubility of calcium, the colloids of urine act in a similar manner.

Neither is there available any evidence that simple crystalluria has an etiologic relationship to the formation of concretions.[3] Crystalluria is a frequent clinical observation and may occur daily in the same individual for many months without the formation of a calculus.

On the basis of our present knowledge we cannot conclude that the formation of an organized calculus is solely, or even primarily,

the result of factors which influence the solubility products of the crystalline substances involved.

ORGANIC MATRIX OF CALCULI

Attempts to Recover the Matrix from Formed Calculi. We have been unable to determine accurately the quantity of organic material which may be considered to form the matrix of calculi. The usual methods for the dissolution of stones with strong mineral acids destroy the matrix and alter that which is recovered to form a gum-like mass of unidentifiable material. The partial dissolution of uric acid calculi in alkaline media has resulted in the leaching out of an organic matrix which contains all of the red-brown pigment characteristic of these stones. The undissolved residue is a soft, putty-like mass of white uric acid. The various colors observed in urinary calculi are an inseparable part of the organic matrix. All crystalline structures yet identified in urinary calculi[21] are normally white.

The most satisfactory method for demonstrating the presence of the organic matrix has been the slow chelation of the calcium ions with ethylene-diaminetetraacetic acid. Some of the organic material so obtained has shown metachromatic staining with aqueous toluidine blue.[14] The fact that the organic material recovered from various large calculi gives a positive Million test, a positive biuret test, a positive periodic acid test (Hotchkiss-McMannus stain) and a positive Molisch test indicates the presence of both protein and carbohydrate. In general, the stones composed primarily of the large, plane-surfaced crystals of calcium oxalate dihydrate have shown the least amount of matrix. The stones composed of mixtures of hydroxyapatite and calcium oxalate monohydrate have shown the greatest quantities of matrix.

None of these methods so far employed has resulted in recovery of a material suitable for complete analysis. Perhaps the recovery of the active mucoprotein matrix from formed calculi is no more feasible than the recovery of the clam's mantle from the nacreous lining of its dead shell.

Recovery of Materials from Urine Which May Form the Matrix of Calculi. A more practical approach may be directly toward a search for a "calcifiable matrix" in the urine of patients who are forming calcigerous urinary stones. A previously described technic[4] was used to recover all the non-diffusible components in twenty-four-hour specimens of urine from three normal subjects and from five patients with urinary calculi. Each residue was placed in a cellophane bag and dialyzed against distilled water until it was free of diffusible salts. These bags were then suspended in a sterile twenty-four-hour specimen of normal urine, which was stored at 1°C. to prevent bacterial growth. The sterile urine was replaced every seventy-two hours by a fresh specimen from the same normal subject. Layers of a firm crystalline material were observed to develop within the colloidal gel recovered from three of the patients with calculous disease, and smaller crystalline deposits were found in the samples from the other two patients with calculous disease. Analysis of these crystals revealed them to contain calcium and phosphate. No crystalline material could be distinguished by gross, microscopic or chemical analysis of the colloidal residues from the normal subjects. Figure 1 is a comparison of the crystalline residues from two patients with calculous disease and the uncrystallized residue from one normal subject. The greatest quantity of crystallization occurred in the colloidal residue from a patient who was subsequently demonstrated to have a functioning adenoma of the parathyroid gland. (Fig. 1A.)

Electrophoretic studies of the urinary proteins were made, and the urine of patients with calculous disease was found to contain a mucoprotein with electrophoretic mobilities different from that of any component of normal urine.[4] When this mucoprotein was suspended in calcifying solutions, there was precipitation of a calcium-mucoprotein chelate and the subsequent formation of a calcium phosphate precipitate.[5]

The aforementioned studies taken together were considered to be at least suggestive evidence that the urine of patients with calcigerous stones contains a "calcifiable matrix." No such material has been demonstrated in normal urine.

The urine of both normal subjects and patients with calculous disease was found to contain a mucoprotein of molecular weight 7×10^6. It is considered to be the principal product of the secretory activity of the urinary epithelium and has been referred to as uromucoid.[5] This material was independently isolated as the virus-inhibitory mucoprotein of urine by Gottschalk[12] of Australia, Odin[19] of Upsalla, and Tamm and Horsfall[25] of New York. It has a

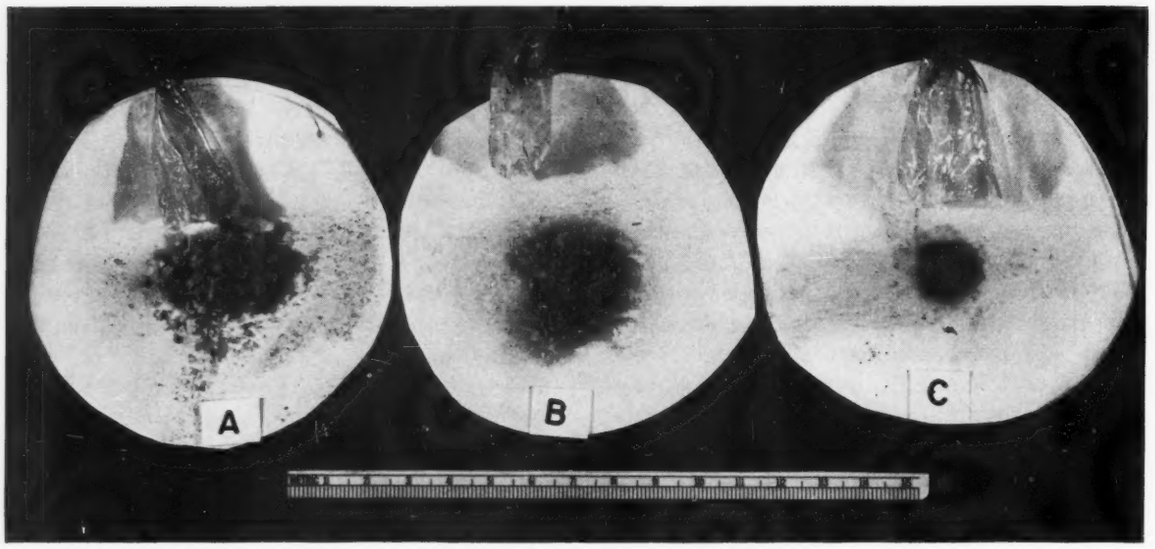


FIG. 1. Crystals containing calcium and phosphate which developed within the "calcifiable matrix" of colloidal material recovered from the urine of patients with growing calcigerous stones of the renal pelves. A, colloidal residue from twenty-four hour urinary output of a patient subsequently proven to have primary hyperparathyroidism. B, twenty-four hour colloidal residue from urine of patient with single renal calculus. C, twenty-four hour colloidal residue from normal control subject; no crystalline material developed in the control preparations. These colloidal residues were dialyzed free of salts and then suspended in cellophane bags in the same twenty-four hour urine specimen from a normal subject. Sterile urine was replaced at seventy-two hour intervals by twenty-four hour specimens from the same normal subject.

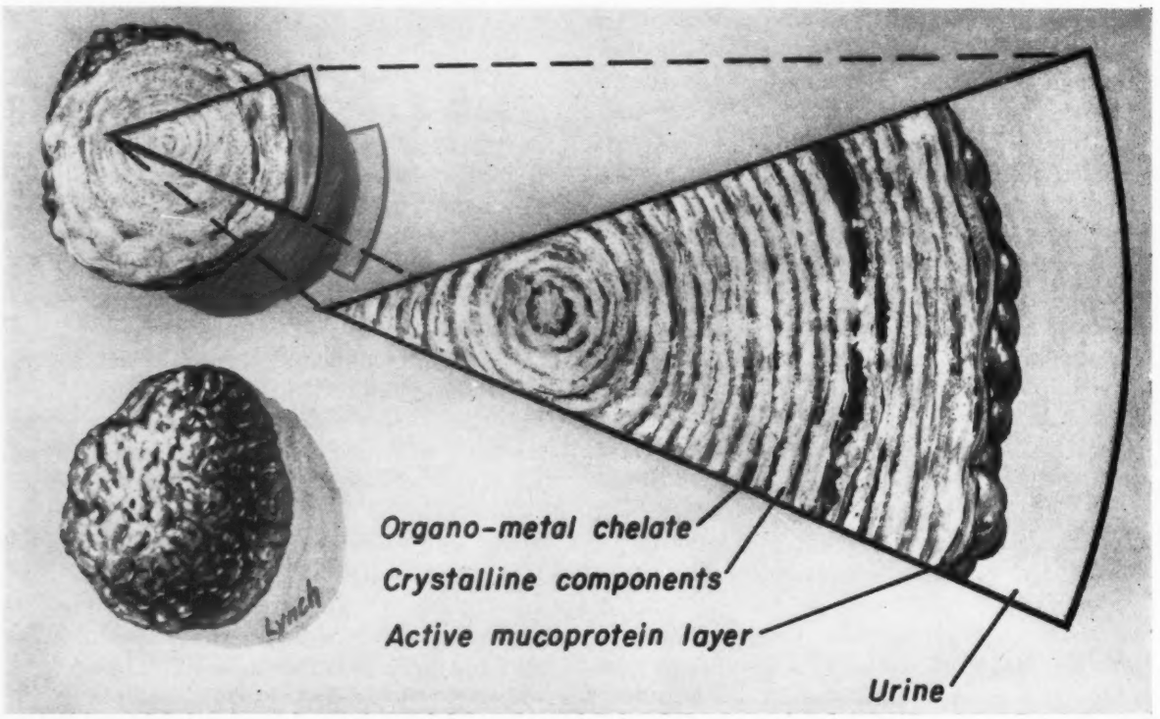


FIG. 2. Structure of a representative calculus removed from the renal pelvis. The center is hydroxyapatite; successive layers are mixtures of crystals of hydroxyapatite and calcium oxalate dihydrate. Dissecting binoculars were utilized for the detailed study.

total carbohydrate content of 25.9 per cent, composed of hexoses (galactose and mannose) 8.3 per cent, hexosamine 7.7 per cent, fucose 1.0 per cent and "sialic acid" 9.8 per cent. This material is quite insoluble in normal urine and in buffer solutions throughout the pH range of normal urine. When suspended in calcifying solutions, it did not produce any appreciable chelation of calcium as determined by conductometry.

This material was found to be soluble in buffer solutions of pH 12.3, which disrupted the molecule into smaller units with a molecular weight in the range of 3,710 to 4,250. These units were sufficiently similar in molecular weight and net negative charge to give electrophoretically homogeneous patterns throughout the pH range of 4.5 to 12.0. Analysis of this material revealed a carbohydrate content of 21.5 per cent, composed of hexose 8.3 per cent, hexosamine 2.3 per cent,

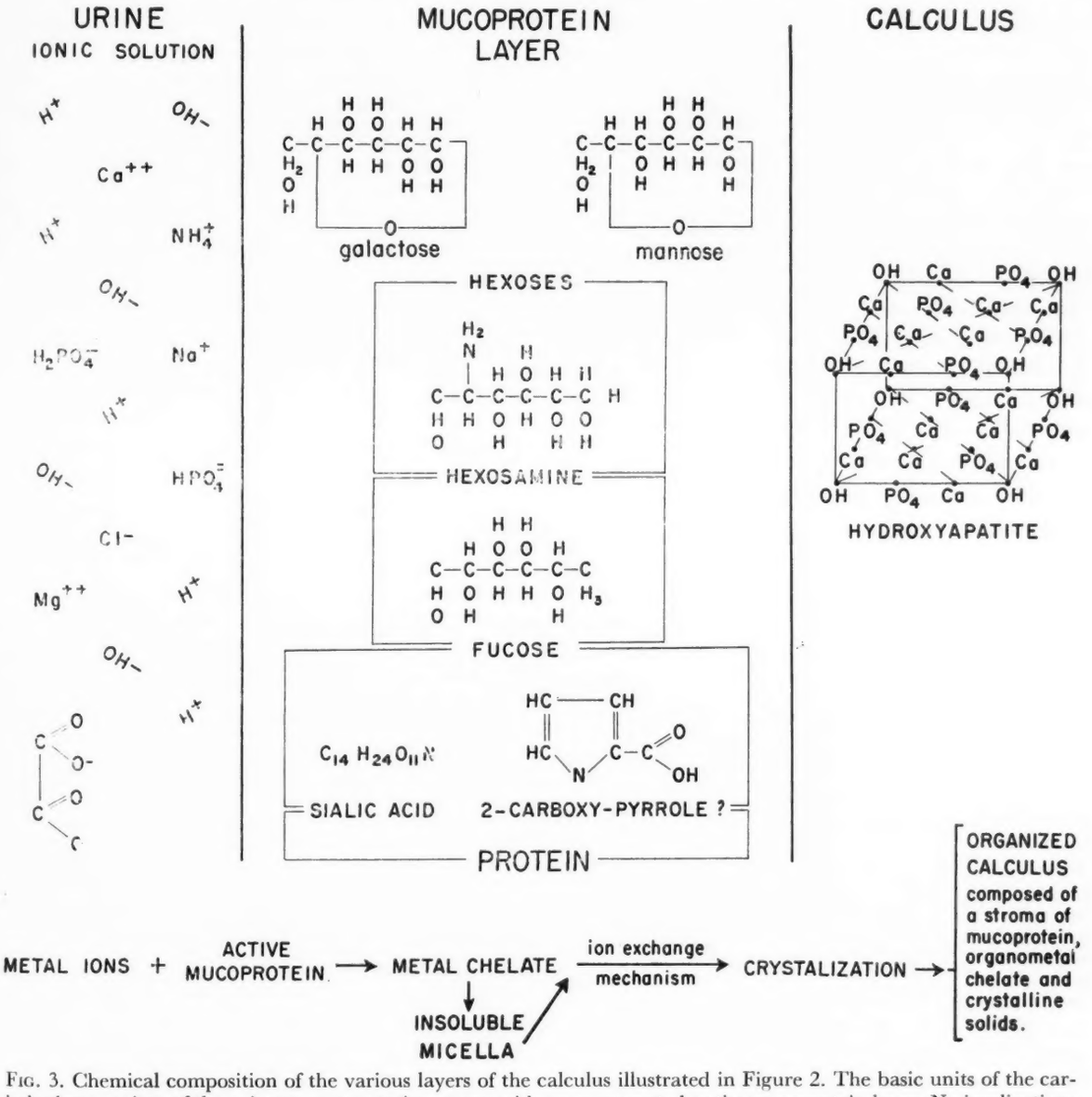
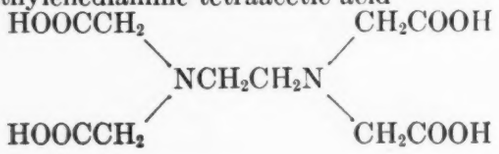


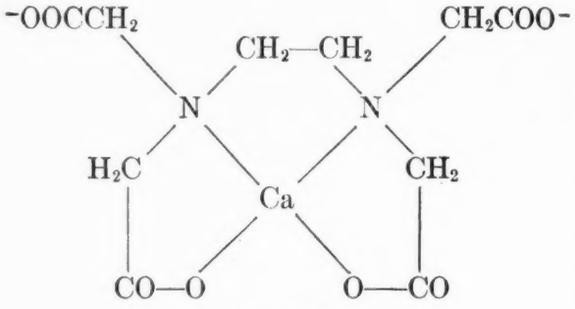
FIG. 3. Chemical composition of the various layers of the calculus illustrated in Figure 2. The basic units of the carbohydrate moiety of the urinary mucoprotein, uromucoid, are represented as the mucoprotein layer. No implications as to the quantitative relationships, structural bonds, optical isomerism or terminal groupings of these sugars are intended. There is evidence that uromucoid contains at least two carbohydrate moieties composed of slightly different combinations of these basic units. The calculus is represented as a basic unit of hydroxyapatite,[22] the most common crystalline component of calculi.

fucose 2.1 per cent and "sialic acid" 8.8 per cent.[6] This soluble form of "uromucoid" was found to bind calcium to form a relatively insoluble calcium-mucoprotein complex. Conductometric and electrophoretic studies indicated this to be an insoluble mucoprotein chelate of calcium.[5]

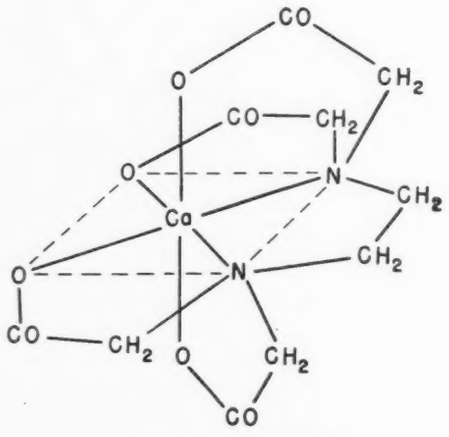
matrix. The exterior is covered with a glistening layer of mucoprotein, varying in thickness from a few hundred microns to several millimeters. Figure 3 is a schematic drawing of the general chemical composition of each of these layers.

Ethylenediamine tetraacetic acid

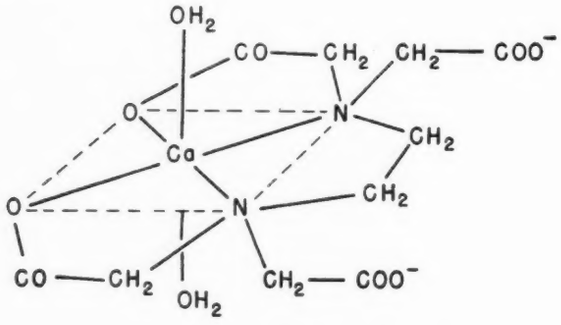




I Quadridentate



II Sexadentate



III Quadridentate

FIG. 4. Calcium chelates of ethylenediamine tetraacetic acid after Martell and Calvin.[17] III illustrates structural arrangement in which calcium with a coordination number of six may unite with a quadridentate chelate compound and still retain a bond relationship with hydroxyl or phosphate ions. Such a structure may be representative of an organic template which facilitates the crystallization of hydroxyapatite by the spatial arrangement of calcium, hydroxyl and phosphate ions.

The possibility thus exists that the "calcifiable matrix" present in the urine of patients with calculous disease is a modified or "activated" form of the uromucoid present in all urine.

INITIATION AND GROWTH OF URINARY CALCULI

Figure 2 is an illustration of the most usual type of renal calculus encountered in our series. The center is composed of calcium phosphate (hydroxyapatite) and the succeeding layers are a mixture of separate apatite and calcium oxalate crystals, with intermingled layers of organic

The carbohydrate fraction of the urinary mucoprotein contains substances which may form chelate compounds with calcium.[17] These include the hydroxy acids of galactose, mannose and fucose, glucosaminic acid and the proline structure, 2-carboxy pyrrole. Only the empirical formula of "sialic acid" has been determined[26] but inspection of this suggests that it probably represents a structure capable of chelate ring formation. (Figs. 3 and 4.) These carbohydrate units are selected from the analysis of "uromucoid;"[6,12,20] however, with the exception of 2-carboxy pyrrole, all of these components are

basic units of the carbohydrate moieties of serum mucoproteins.[26] For our present illustration it is thus irrelevant whether we ascribe these units to uromucoid or to a mucoprotein derived from the serum.

In any consideration of the solubility or ion exchange reactions of calcium and other metals, the chelate compounds are of peculiar importance. A metal chelate compound is a single molecule containing two or more electron donor groups which bind the metal ion to form an undissociated ring compound in which the metal is an integral unit. The divalent calcium ion has a coordination number of at least four and probably six. (Fig. 4.) A single quadridentate chelate molecule can thus tie up a calcium ion in three individual rings through four of these coordinate covalent bonds; or, conversely, a single calcium ion can tie up two molecules of a tridentate chelate compound, forming four rings through six bonds. Oxalic acid is an example of a simple bidentate chelate compound.

The physical and chemical properties of metal chelates are quite different from those of the metal salts, metal complexes or organometallic compounds. Calcium firmly caught in the grip of these chelate rings is no longer active in the same sense as ionized calcium in a similar solution. This fact is evidenced by alterations in electrical conductivity and electrophoretic properties, in solubility and in the production of color reactions, as well as a great many other properties.[17]

Although the metal ion is firmly trapped in the chelate ring system, it may be separated with extreme rapidity under certain conditions. Each organo-metal chelate has a definite stability constant, and a given metal can be readily displaced from the chelate structure by other metals higher in the series. The presence of competitive chelate structures, the hydrogen ion concentration, and a variety of diverse factors influence this separation of the metal from its chelate.[17] These properties have made the metal chelate compounds most valuable for removing lead from the human body,[23] providing soluble minerals for plant nutrition and separating complex mixtures of metal ions.

Most of the metal chelate compounds studied to date have their greatest usefulness in the formation of highly soluble metal chelates. The mucoproteins of urine are characterized by having the chelate rings firmly attached to a protein moiety, and the calcium chelates thus formed tend to be highly insoluble macromolecules.[5] The significance of this property in the formation of urinary concretions is immediately apparent. An active chelate compound of this type can form an insoluble calcium-mucoprotein molecule by chelating calcium from urine which contains even minimal quantities of calcium. If this complex remains adherent to the walls of the urinary tract, a very high local concentration of calcium may be built up in normal urine. Thus a colloidal micelle[13] of extremely high calcium content may develop.

Under the influence of shifts in hydrogen ion concentration, the presence of oxalic acid, orthophosphates or particularly condensed phosphates, or other changes in environment,[17] the chelate rings may be induced to release calcium, with the resultant local formation of crystalline calcium compounds. In the initial stages these crystals may form adjacent to the mucoprotein or within its meshes; but as the process repeats itself many times, the successive layers of crystal units will tend to form on the surface of the pre-existing crystal. The structure may thus become a calculus, with the layers oriented as shown in Figure 2.

As successive layers of crystalline material are laid down upon the surface of the calculus, variable quantities of the mucoprotein layer may be left entrapped to form the "matrix." However, the point of growth of the stone is at the surface of the crystalline layer and immediately beneath the surface of the mucoprotein cover. Thus the growth of calculi may be likened mechanically to the growth of the oyster's shell as the mantle lays down successive layers of nacre.

COMMENT

It is apparent that the mucoprotein responsible for this transfer of ions from urine to crystalline solid must be different from any found in normal urine, and we have used the term "activated mucoprotein" to denote this difference. We have been unable to demonstrate any such activity in any of the proteins found in normal urine.[5] If "uromucoid" is the responsible mucoprotein, its structure must be modified in some manner to free the carboxyl and amino groups which are probably responsible for calcium chelate formation. It seems unlikely that hydrogen bonds alone could tie up these groups to the exclusion of calcium, since the stability constants of most such structures are

considerably less for hydrogen than for calcium. It is more likely that some internal arrangement of the carbohydrate moiety prevents the chelation of calcium until the structure has been rearranged or disrupted. The observation that uromucoid is a much more active chelating agent for calcium after its molecule has been degraded and a portion of the hexosamine content split away lends support to this latter concept.

A coating of normal uromucoid might be expected to form a protective inert layer which could limit the growth of the crystalline components of calculi. Such a layer of inactive normal uromucoid may account for the molding of branched calculi to conform to the outlines of the epithelium-lined renal pelvis and calyces. The tendency for "staghorn" calculi to fill the renal pelvis rapidly and then remain quiescent may also result from this contact with the secretions from relatively normal epithelium.

We have frequently observed clusters of the large plane-surfaced crystals of calcium oxalate dihydrate on the surfaces of calculi such as the one shown in Figure 2. These deposits may be the result of crystallization of this material on a large surface without the intervention of a chelate mucoprotein step. However, at least half of the "pure" calcium oxalate stones listed in Table I have a discernible nucleus of calcium phosphate. It is probable that the remainder have a microscopic nidus of calcium-mucoprotein chelate, with or without phosphatic crystals. The occurrence of magnesium ammonium phosphate crystals in calculi may represent a similar type of "secondary deposit" or surface crystallization; however, chelate agents for calcium will also chelate magnesium if the local conditions are favorable and if all available calcium has been previously bound.

SUMMARY

Considerable evidence has accumulated which would indicate that the organic matrix of urinary calculi plays an active part in the local concentration and precipitation of calcium. This metal is the principal cationic unit in the crystalline structure of more than 90 per cent of all urinary concretions. It is suggested that the abnormal (activated) mucoproteins of urine[5] chelate calcium from solution to form relatively insoluble micelles[13] of colloidal calcium-mucoprotein units. This is the initial step in calcigerous stone formation and is followed by crystallization within the meshes of the mucoprotein micella. These same mucoproteins, forming a surface layer, may produce a local concentration of calcium on the surface of the growing concretion. They may even serve as an organic template to facilitate the spatial arrangement of calcium and hydroxyl ions[17] in the growth of the apatite lattice.[22]

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Seminars on Carbohydrate Metabolism

The Metabolism of Carbohydrates*

A Review

DeWitt Stetten, Jr. *and* Yale J. Topper
Bethesda, Maryland

The present paper is intended to give background information in the area of mammalian carbohydrate metabolism. Similar contributions from other sources are expected to appear subsequently in this Journal treating with endocrine regulation and clinical disturbances of sugar metabolism. It is our intent to supply the necessary information relating to the biochemical reactions of the common sugars as these are currently understood. This will permit the future development by other contributors to this series of such matters as the regulation of carbohydrate metabolism by endocrine mechanisms and the metabolic defects in the diseases of carbohydrate metabolism.

The benefits which the mammalian cell derives from its nutrients may be divided into two classes. (1) All of the compounds necessary for its continued survival and the performance of its normal function must come to the cell from the nutrient directly or must be synthesized from precursors which are supplied in this nutrient. Included in this category is the need for continuous replacement within the architecture of the cell of those structural components which are being destroyed. (2) All of the energy required for the continued survival and operation of the cell must be derived from the breakdown of energy-containing compounds of the nutrient.

The present discussion of carbohydrate metabolism will be oriented toward a consideration of the compounds which the cell can form from the sugars which are supplied to it and of the sources of the energy and the mechanisms of its release or storage in the course of carbohydrate catabolism.

Photosynthesis and the Origins of Biochemical Energy. The prime mover with respect to the energy of biochemical reactions is the phenomenon of photosynthesis. Ultimately, all the energy with which we are concerned is derived from that portion of the solar spectrum that is absorbed by chlorophyll. In green plants this dependence is fairly direct; in animals this dependence, though less immediate, is equally real. Photosynthesis may be defined as the reductive fixation of carbon dioxide into organic molecules with the liberation of oxygen gas, brought about by the action of light:

$$H_2O + CO_2 \xrightarrow{\text{light}} \underset{\text{(carbohydrate)}}{1/n\,(CH_2O)_n} + O_2\uparrow \quad (1)$$

This process has been bisected into two major steps, only the first of which is photodependent:

$$\underset{\text{(electron acceptor)}}{H_2O + X} \xrightarrow{\text{light}} \underset{\text{(active oxygen)}}{H_2X + [O]} \rightarrow \tfrac{1}{2}\,O_2\uparrow \quad (2)$$

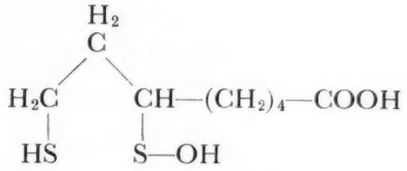
In this, the so-called "light" reaction, water is cleaved in the presence of an electron acceptor, X, to yield a reduction product, H_2X, and oxygen.

By means of this photo-energized reaction the energy of certain electrons is enormously en-

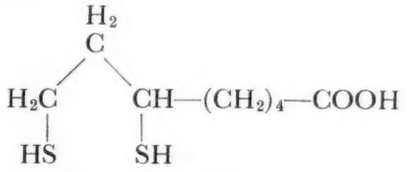
* From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, United States Department of Health, Education and Welfare, Bethesda, Md.

hanced as they are delivered, in a single step, from the stable, low energy condition which they occupy in water to a high energy condition which they occupy in the reduced cofactor H_2X. The fixation of CO_2 is a secondary process not, *per se*, photodependent.

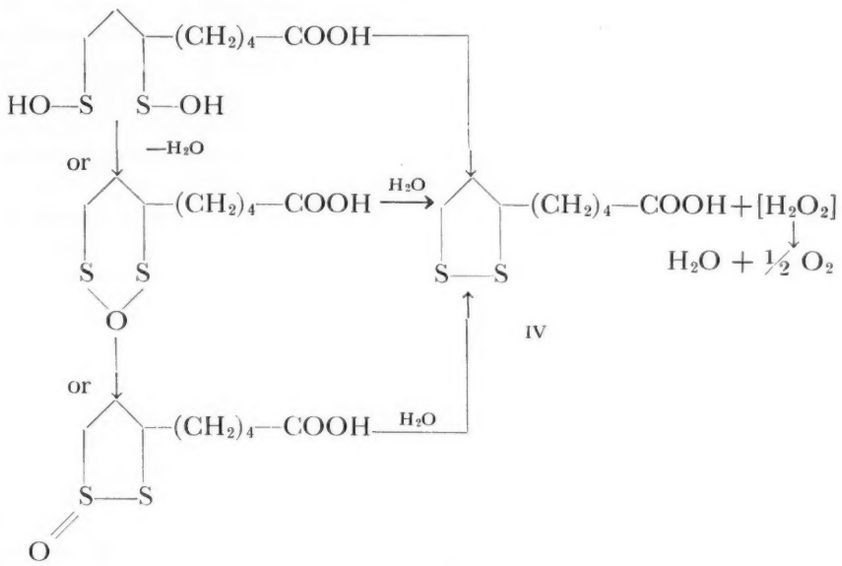
During the catabolic, exergonic phase, which occurs in green plants when the light is turned off and in mammalian cells at all times, the energy of electrons cascades downward, not in a single step which would be explosive and wasteful but in many small discrete steps until the basal energy level of water is again achieved. The generation of CO_2, like its fixation, is a secondary process involving the decarboxylation of keto acids formed incidentally by the various oxidative processes.



Two molecules of this product then dismute to yield (III):

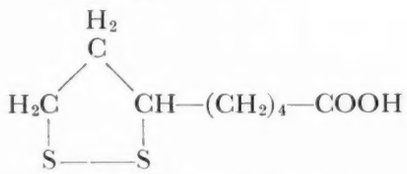


which is H_2X (equation *2*), and a product (IV) which may be termed the active oxygen (equation *2*):



(*3*)

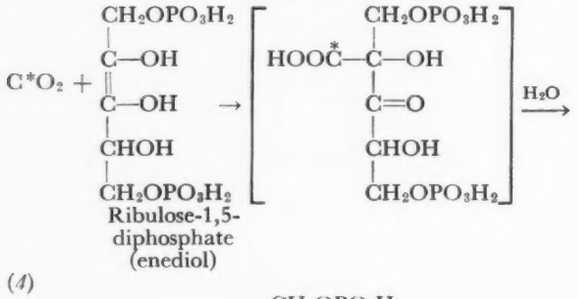
Recently, the probable nature of X in equation *2* has been elucidated. It is lipoic acid, having the structure (I):



The essential role of this compound in the oxidation of pyruvic acid and its entry into the Krebs tricarboxylic acid cycle had been recognized long before its structure was known. When chlorophyll is excited by light it is pictured as passing energy on to lipoic acid, the strained five-membered ring of which reacts with water to yield a thiolsulfenic acid of the type (II):

The net result of this total process is to decrease the concentration of the cyclic lipoic acid (I). Since this compound is essential for oxidation, via the Krebs cycle, of pyruvic acid, herein lies the probable explanation for the fact that during photosynthesis the Krebs cycle in plants is essentially non-operative.

As indicated earlier, the fixation of carbon dioxide is itself not photodependent but is linked to the reductive pressure which stems from the photosynthetic generation of reduced coenzymes. The probable initial steps of CO_2 fixation by green plants include condensation with the ketopentose, ribulose-1,5-diphosphate, and subsequent cleavage of the product to yield 2 molecules of 3-phosphoglyceric acid:



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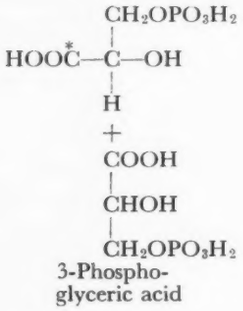


The location of the radioactivity initially incorporated by green plants photosynthesizing in an atmosphere of $C^{14}O_2$ has been shown to be in the carboxyl carbon of 3-phosphoglyceric acid (v):

$$H_2O_3PO—CH_2—CHOH—C^{14}OOH$$

The continued operation of this reaction requires the regeneration of five-carbon sugars and essential for this is the reduction of phosphoglyceric acid to the triose phosphate, 3-phosphoglyceraldehyde (vi):

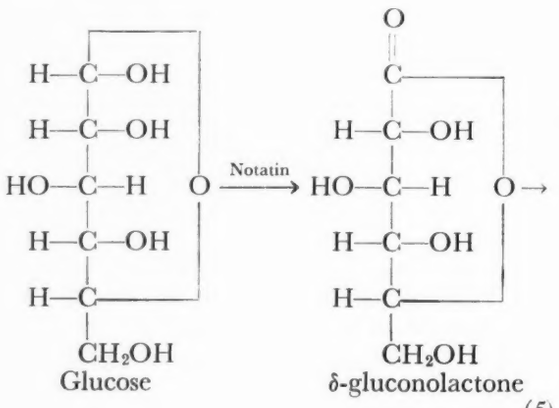
$$H_2O_3PO—CH_2—CHOH—CHO$$

Whereas the immediate source of hydrogen for this reduction is probably reduced diphosphopyridine nucleotide, DPNH, the ultimate source of hydrogen is doubtlessly reduced lipoic acid (iii).

The triose phosphate generated serves as a source of hexoses such as glucose by reversal of the Embden-Meyerhof pathway, which is to be discussed in the next section. It also permits regeneration of the pentose, ribulose, required in reaction *4*. The details of these routes are beyond the scope of this review but it may be mentioned that a prominent pathway for pentose formation is the reversal of a portion of the transketolase pathway, described on page 102.

Glycolysis via the Pathway of Embden and Meyerhof. For the energy that is contained in the glucose molecule to become available to the mammalian cells which consume it, the bonds holding the molecule together must be broken. In the respiring organism the final products of such breakdown are generally CO_2 and H_2O. It has been found that this process occurs over fairly well defined pathways, some of which are common to a variety of cells and tissues. Of these the most studied is that referred to as the Embden-Meyerhof pathway, a series of reactions whereby glucose is degraded to lactic or pyruvic acid or both. Among the many fates of pyruvic acid is its introduction into the citric acid cycle of Krebs, whereby it is finally oxidized to carbon dioxide and water. However, since the citric acid cycle is common to metabolites of lipids and amino acids as well as to those from carbohydrate sources, it will not be considered as falling within the area of this review.

The reaction which initiates the Embden-Meyerhof sequence, and probably the most commonly occurring of the metabolic fates of glucose in the mammal, is phosphorylation in position 6. Non-phosphorylating fates of glucose do occur in microbial biochemistry and the best known example of these is the notatin reaction:



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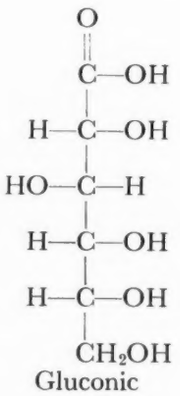
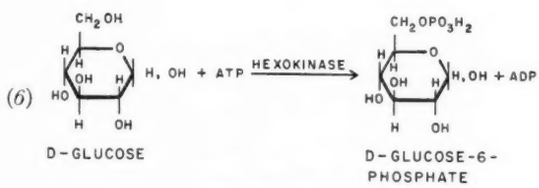


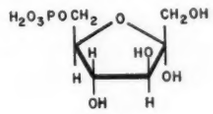
A by-product of this reaction is hydrogen peroxide, which is apparently the product responsible for the bactericidal action of notatin. A number of years ago a similar reaction was discovered in mammalian liver wherein glucose was dehydrogenated by DPN to yield gluconolactone. However, the significance of this reaction in the glucose economy of the intact mammal is questionable.

Glucose phosphorylation is a ubiquitous reaction in animals and in microbes. The unique source of phosphate is adenosine triphosphate, and the enzyme is termed hexokinase. This enzyme occupies a key position in glucose catabolism and was the enzyme implicated by Cori as related to the mode of action of anterior pituitary extracts and of insulin. Essentially all cells of higher animals have the capacity to phosphorylate glucose, but hexokinases from various sources differ in their specificities with respect to the sugar component. Some, such as intestinal mucosa hexokinase, effect phosphorylation of galactose and fructose as well as glucose, while others, such as a particular hexokinase of muscle and liver, operate solely upon fructose to give fructose-1-phosphate. The over-all reaction



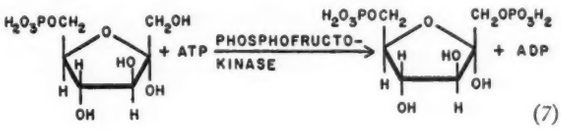
is exergonic and essentially irreversible. One mole of energy-rich phosphate in the form of ATP is expended for each mole of glucose phosphorylated.

The product, D-glucose-6-phosphate, has four important fates open to it: (1) Under the influence of a specific glucose-6-phosphatase it may be irreversibly hydrolyzed to yield glucose and inorganic orthophosphate. This reaction does not occur in muscle but is known to occur in liver and probably also occurs in kidney, intestinal mucosa and other tissues. It is the immediate source of the bulk of the biosynthetic blood glucose. (2) Glucose-6-phosphate may be transformed to glucose-1-phosphate. This reaction and its consequences are discussed on page 106. (3) Glucose-6-phosphate may be oxidized to 6-phosphogluconic acid. The implications of this reaction appear on page 102. (4) Glucose-6-phosphate may be reversibly isomerized to fructose-6-phosphate (VII):



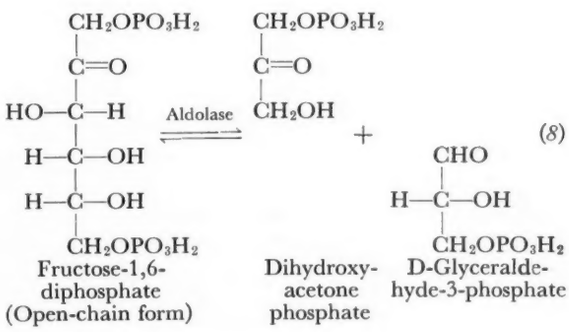
The enzyme for this transformation is termed phosphoglucose isomerase and the product is on the main path of the Embden-Meyerhof sequence. This same product may also arise from fructose directly by phosphorylation with ATP and fructokinase of yeast, brain or muscle.

Further phosphorylation of fructose-6-phosphate consumes a second mole of energy-rich phosphate and yields fructose-1,6-diphosphate as a product:



This reaction, like the hexokinase reaction, is exergonic and irreversible. There does, however, appear to be a phosphatase capable of catalyzing the hydrolysis of fructose diphosphate to fructose-6-phosphate and inorganic phosphate.

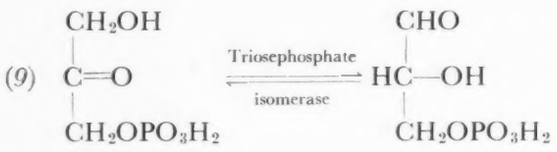
The next reaction in the Embden-Meyerhof sequence is a reversible cleavage of the bond between the two central carbon atoms 3 and 4 of the hexose skeleton:



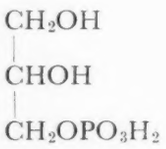
The products of this reaction in the catabolic sense are the phosphoric acid esters of the ketotriose, dihydroxyacetone, and the aldotriose, glyceraldehyde. In the synthetic or anabolic

sense, the enzyme aldolase is remarkably specific with respect to dihydroxyacetone phosphate but a variety of aldehydes have been found to replace glyceraldehyde-3-phosphate, leading to the possible synthesis of a variety of sugars. The synthetic possibilities of this enzyme have only recently been generally appreciated.

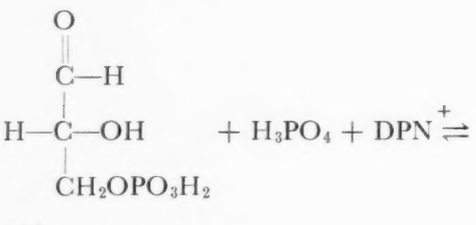
The two triose phosphates are readily interconvertible in the presence of triosephosphate isomerase and are often considered as an equilibrium mixture:



Dihydroxyacetone phosphate is of interest as the source of glycerol and α-glycerolphosphoric acid (VIII)



to which it is readily reduced by DPNH, and these products undoubtedly participate in the synthesis of neutral fats. Glyceraldehyde-3-phosphate is subject to a remarkable oxidation involving the obligatory participation of inorganic phosphate. The details of this reaction, which involves a sulfhydryl enzyme and oxidized diphosphopyridine nucleotide, are currently unclear but the over-all stoichiometry is expressed by the equation:



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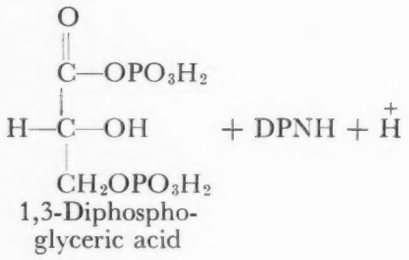
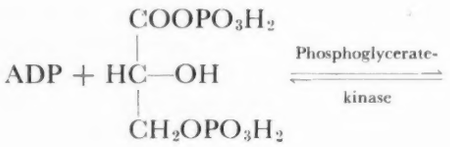
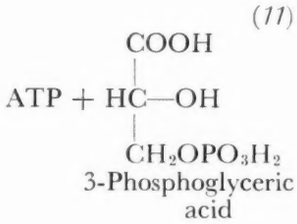


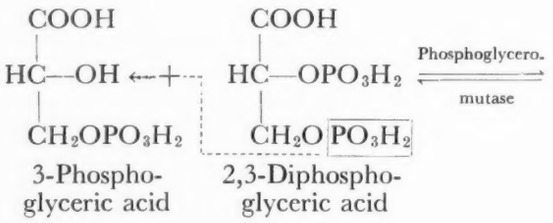
This reaction is unusual in two important regards. In the first place, it is the sole step intervening between glucose and pyruvic acid in this sequence which involves oxido-reduction. Secondly, it is a reaction whereby inorganic orthophosphate is consumed while an energy-rich phosphate bond, —C(=O)—OPO_3H_2, is generated. The phosphate in position 1 of the product is of sufficiently high energy to enter the adenosine triphosphate system:



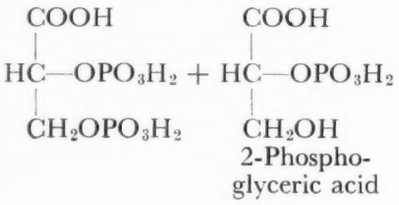
(11)



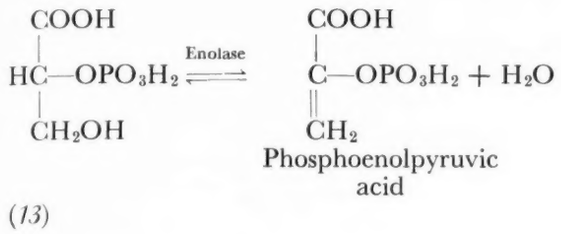
The product of this reaction is in equilibrium with its isomer, 2-phosphoglyceric acid, and since the reaction is accelerated by the presence of 2,3-diphosphoglyceric acid a mechanism analogous to that of the phosphoglucomutase reaction (page 106) has been postulated:



(12)

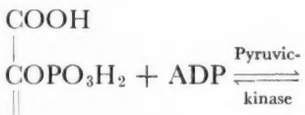


In the presence of enolase, 2-phosphoglyceric acid loses a mole of water:



(*13*)

to yield the phosphoric acid ester of (enol) pyruvic acid. Phosphate in this situation is also rich in energy and capable of entering the ATP system:



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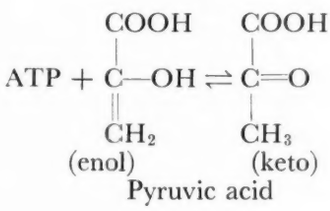


In the course of its normal operation in respiring tissues a large part of the pyruvic acid formed undergoes oxidative decarboxylation to yield acetyl-coenzyme A. This important product is a precursor for synthesis of fatty acids, sterols, and so on, and for CO_2 via the Krebs tricarboxylic acid cycle. Pyruvic acid is also an acceptor of amino groups to yield alanine and an acceptor of CO_2 to yield oxaloacetic acid. When oxygen is unavailable the reduced DPNH formed in the phosphoglyceraldehyde dehydrogenase reaction reduces pyruvic to lactic acid, which then is the stable final product of so-called "anaerobic glycolysis." With normal oxygen tensions in mammalian tissue, very little lactic acid accumulates and pyruvic acid may be considered to be the terminus of the Embden-Meyerhof sequence.

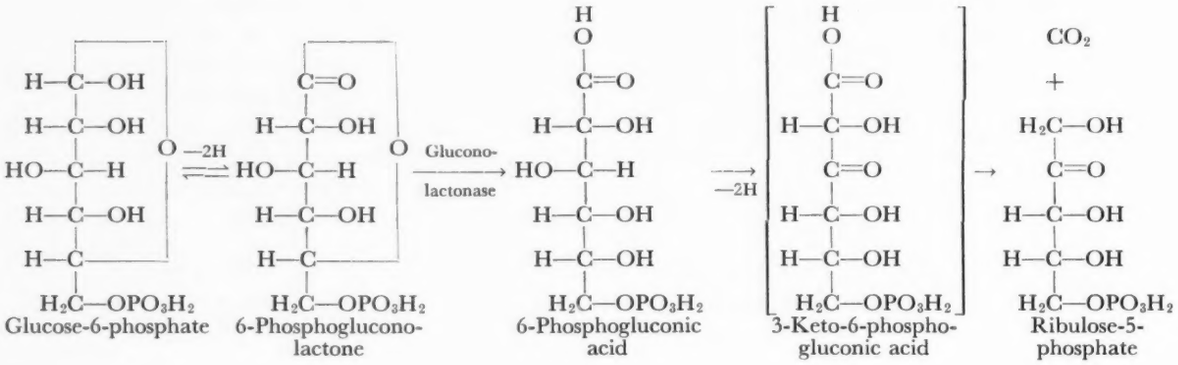
The gross energy yield liberated when a mole of glucose is broken down to two moles of lactate is approximately 58,000 calories, which is a small fraction of the energy yield, 686,000 calories, of the total oxidation of glucose to CO_2 and H_2O. In the course of the process some energy is conserved, as the following accounting of high-energy phosphate (~P) will reveal:

	~P Yield
glucose → glucose-6-phosphate	−1
fructose-6-phosphate → fructose-1,6-diphosphate	−1
2(diphosphoglyceric acid) → 2(phosphoglyceric acid)	+2
2(phosphopyruvate) → 2(pyruvate)	+2
Yield: moles ~P per mole glucose	+2

The Embden-Meyerhof pathway, with minor modifications, appears to operate in all mammalian tissues. It is the sole recognized pathway of glucose breakdown in muscle and is a major pathway in many other tissues, such as brain.

Glucose Oxidation via 6-phosphogluconic Acid. Whereas the pathway of Embden and Meyerhof has, until recently, been considered as the prototype which, subject to minor modifications, described the utilization of glucose, growing evidence for the existence of a distinct and alternative pathway has accumulated in the past few years. This route has variously been called the "hexose monophosphate shunt," the "direct oxidative pathway" and the "Warburg-Lipmann-Dickens pathway" but is perhaps most appropriately termed the "phosphogluconate oxidation pathway." It stems, as does the Embden-Meyerhof pathway, from glucose-6-phosphate and is initiated by a series of oxidative steps. See formula (*15*), page 102.

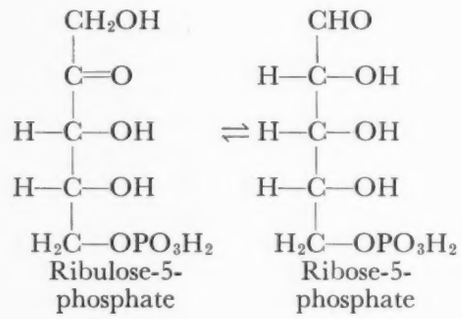
In each of the two oxidative steps triphosphopyridine nucleotide serves as hydrogen acceptor. The enzyme for the first reaction of the series, glucose-6-phosphate dehydrogenase, was named "Zwischenferment" by Warburg many years ago. The second enzyme, 6-phosphogluconate dehydrogenase, is believed to oxidize the sugar at carbon atom 3 but the 3-keto acid, the postulated product, has not been definitively characterized. Carbon 1 of glucose is then



(*15*)

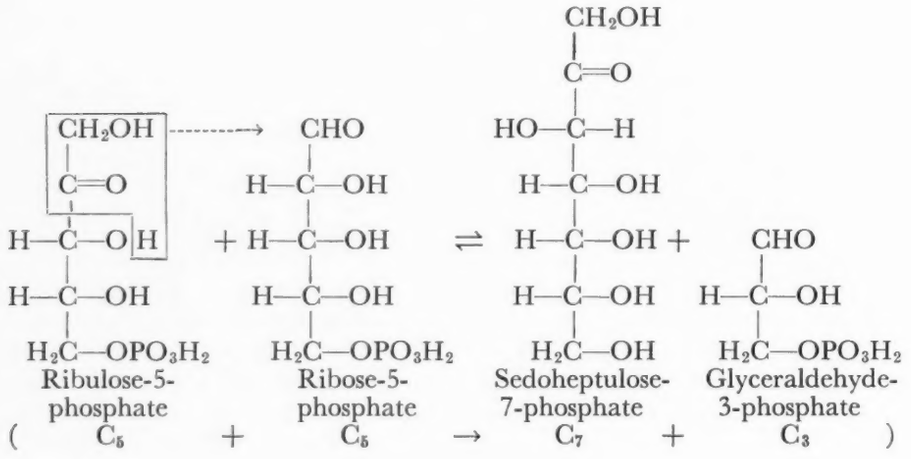
eliminated as CO_2 yielding a pentose, ribulose-5-phosphate.

The action of a phosphopentose isomerase, acting analogously to phosphohexose isomerase (page 104), brings the ketopentose and the aldopentose into equilibrium:

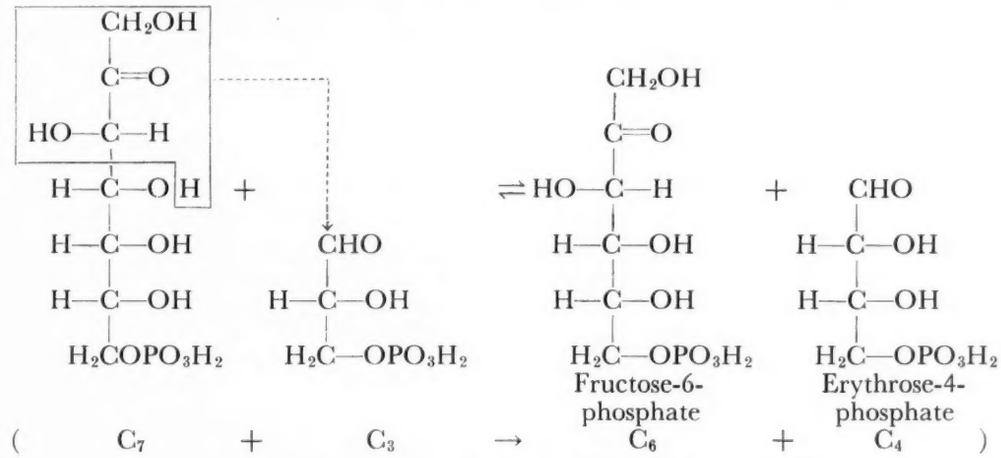


Ribose-5-phosphate may be activated at position 1 by reaction with ATP to yield 5-phosphoribose-1-pyrophosphate, and this product serves as a source of pentose in the synthesis of ribose nucleotides and ribose nucleic acids. Alternatively, ribose-5-phosphate is subject to transformation to ribose-1-phosphate by a mutase mechanism comparable to that in the hexose series and this derivative may also serve as a source of pentose in the synthesis of ribose nucleosides.

Carbon atoms 1 and 2 of ribulose are quite reactive. In the process of photosynthesis it is this pair of carbon atoms which ultimately accepts CO_2 from the atmosphere to yield phosphoglyceric acid. This pair of carbon atoms is of interest to us in another respect. The enzyme transketolase can, in the presence of thiamine pyrophosphate, transfer these carbon atoms, in the form of enzyme-bound glycolaldehyde ($HOCH_2CHO$), from ribulose-5-phosphate to certain acceptors among which is ribose-5-phosphate:

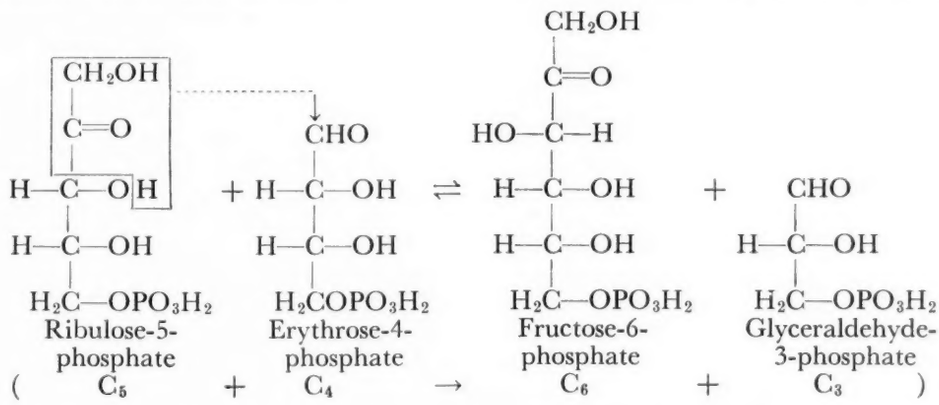


The seven-carbon sugar, sedoheptulose phosphate, may in turn react with the three-carbon sugar, glyceraldehyde phosphate, in a transaldolase reaction involving transfer of the top 3 carbon atoms from the former to the latter:



(*18*)

The metabolic relations of fructose-6-phosphate have already been discussed (page 99). The four carbon sugar fragment may serve, much as ribose-phosphate does, as an acceptor of active glycolaldehyde in a transketolase reaction:



(*19*)

In considering the cyclic operation of this series of reactions one additional fact should be borne in mind, namely, that glyceraldehyde-3-phosphate, by reversal of the steps of the Embden-Meyerhof sequence, may be converted to hexose ($C_3 \rightarrow \frac{1}{2}\ C_6$). Summation of these several steps reveals the following:

	$3\ C_6 \rightarrow$	$3\ C_5 +$	$3\ C_1\ (CO_2)$
	$2\ C_5 \rightarrow$	$C_7 +$	C_3
$C_7 +$	$C_3 \rightarrow$	$C_6 +$	C_4
$C_5 +$	$C_4 \rightarrow$	$C_6 +$	C_3
	$C_3 \rightarrow$	$\frac{1}{2}\ C_6$	
Sum:	$3\ C_6 \rightarrow$	$2\frac{1}{2}\ C_6 +$	$3C_1$

In other words 3 molecules of CO_2 are generated from 3 molecules of glucose with the potential capacity for regeneration of $2\frac{1}{2}$ molecules of hexose.

It is interesting to compare and contrast this pathway with the Embden-Meyerhof pathway. In the phosphogluconate oxidation pathway, beginning with glucose-6-phosphate, no ATP is required but an obligatory oxidation occurs early in the reaction sequence. Repeated operation of the cycle as delineated yields CO_2 as the sole and final product, with release of all the energy introduced into the glucose molecule by photosynthesis. Concerning the disposition and possible conservation of this energy, there is no definitive information. The Embden-Meyerhof pathway, on the other hand, when beginning with glucose-6-phosphate, consumes ATP in the formation of hexose diphosphate. If lactic acid is the accumulated end product, no net oxidation has occurred and the sequence can and does proceed anaerobically. Terminating at lactic acid, this sequence releases only a fraction of the energy contained in glucose.

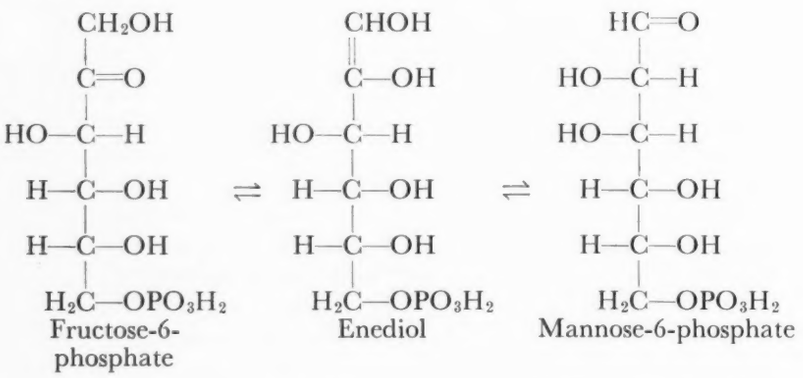
The steps of the phosphogluconate oxidation pathway were, in many cases, first studied in microbial systems. However, there is good reason to suppose that the same or very similar steps also occur in certain mammalian systems. Whereas skeletal muscle appears to catabolize glucose exclusively over the steps of the Embden-Meyerhof pathway, the phosphogluconate oxidation pathway has been shown to operate in liver, mammary gland, testis and certain other tissues.

It would be erroneous to conclude that the two pathways described here for glucose catabolism necessarily are the only pathways that occur. Other routes have been indicated but the evidence in support of their occurrence in mammalian systems is thus far lacking.

Hexose Interconversions. In addition to the various pathways for glucose catabolism involving rupture of the hexose carbon skeleton, there are means available to the organism whereby it can convert glucose into other hexoses with retention of the intact carbon chain. Such reactions lead to the formation of certain monosaccharides which are required for the biosynthesis of lactose and mucopolysaccharides, and to others which are necessary for detoxication mechanisms.

The interconversion of glucose-6-phosphate and fructose-6-phosphate catalyzed by phosphoglucose isomerase has been described on page 99. Mannose, which differs from glucose in its configuration about carbon atom 2 and is found in nature as a constituent of various polysaccharides and of glycoproteins, can be formed as its 6-phosphate ester from fructose-6-phosphate in a reaction catalyzed by a phosphomannose isomerase present in muscle:

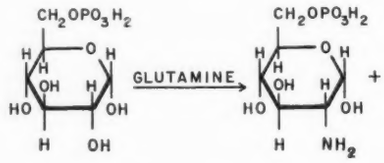
(*20*)



Fructose-6-phosphate — Enediol — Mannose-6-phosphate

Mechanistically, this reaction, which is similar to that for the interconversion of glucose- and fructose-6-phosphates, involves the intermediary formation of an enediol, and consequently the open forms of the sugars are directly implicated. It should be noted that fructose-6-phosphate is an obligatory intermediate between glucose- and mannose-6-phosphates.

The synthesis of glucosamine, which occurs as its N-acetyl derivative chiefly in polysaccharides of the tissues, was first demonstrated with an extract of Neurospora mycelia:

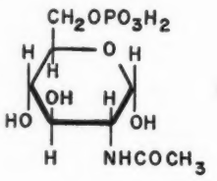


(*21*)

D-Glucose-6-Phosphate — D-Glucosamine-6-Phosphate

At least two further enzymatic reactions intervene between the formation of this product and the incorporation of the glucosamine moiety into mucopolysaccharides:

D-Glucosamine-6-phosphate $\xrightarrow[\text{Coenzyme-A}]{\text{Acetyl-}}$

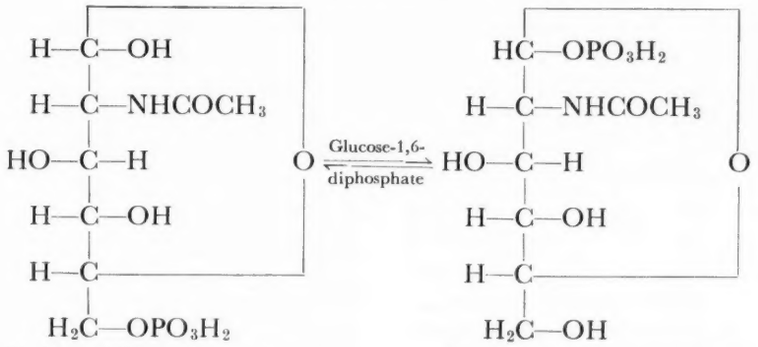


(*22*)

N-acetyl-D-glucosamine-6-phosphate

Mechanistically, this reaction, which is similar to that for the interconversion of glucose- and fructose-6-phosphates, involves the intermediary

The acetylated material is then isomerized to the 1-phosphate in a manner reminiscent of the phosphoglucomutase reaction discussed on page 106.

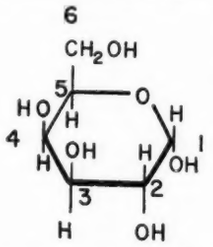


N-Acetyl-D-glucosamine-6-phosphate

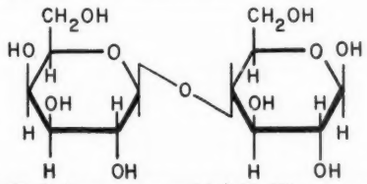
N-Acetyl-D-glucosamine-1-phosphate

(*23*)

Another aldohexose of biochemical interest is D-galactose (IX), which differs from glucose in its configuration about carbon atom 4.

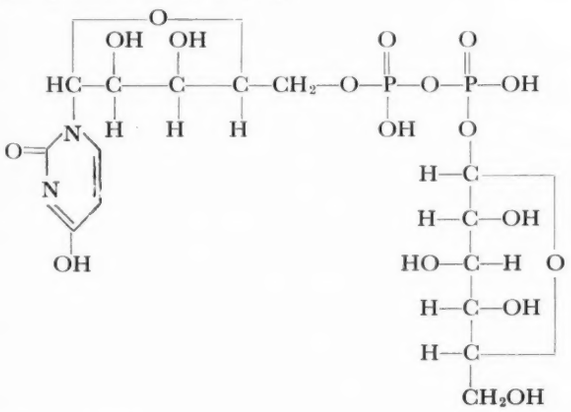


This sugar is a component of several polysaccharides, and of the disaccharide lactose (X), a sugar peculiar to mammals.



4-(β-D-Galactopyranosido)-D-Glucopyranose
β-D-Lactose

Actually glucose-1-phosphate and galactose-1-phosphate are interconvertible, that is, inversion about carbon atom 4 is reversible in the presence of the enzyme phosphogalactose isomerase. The coenzyme for this reaction is uridine diphosphoglucose, UDPG (XI),



and the following steps have been shown to occur:

Glucose-1-phosphate + Uridine triphosphate $\rightleftharpoons$ (UTP)

UDPG + Pyrophosphate

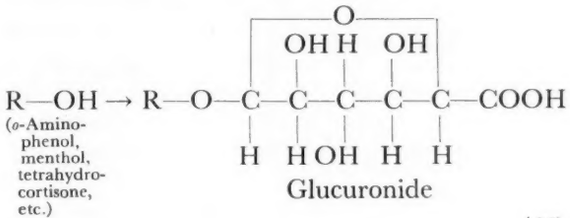
$\uparrow\downarrow$ Phosphogalactose isomerase

UDPGalactose $\underset{\text{(UTP)}}{\rightleftharpoons}$ Galactose-1-phosphate

(*24*)

Little is known of the mechanism of this isomerization other than the fact that it occurs without rearrangement of the carbon skeleton. It should be noted that galactose-1-phosphate can also arise in liver from galactose and ATP by a galactokinase-catalyzed reaction.

Another series of conversions which has been recently elucidated involves the formation of glucuronic acid and its conjugation with certain alcohols to form glucuronides:



(*25*)

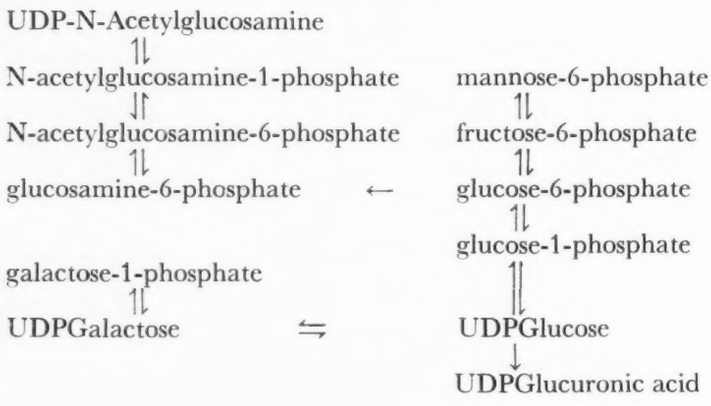
Products of this type of detoxication reaction are excreted in the urine. The oxidation of carbon atom 6 of glucose to give the uronic acid again involves the remarkable coenzyme UDPGlucose and a DPN-linked enzyme derived from liver:

UDPGlucose + 2 DPN^+ $\rightarrow$

UDPGlucuronic Acid + 2 DPNH + $2H^+$ (*26*)
(UDPGA)

"Active" glucuronic acid, UDPGA, then acts as the glucuronide donor in the synthesis of the conjugates. This reaction, which is catalyzed by an enzyme derived from the microsomes of liver, has been demonstrated in the formation of glucuronides of *o*-aminophenol, menthol and tetrahydrocortisone. Although demonstration of the specificity of the enzyme system involved must await purification of the microsomal preparation, the glucuronide conjugating reaction involving UDPGA appears to be a general mechanism for the formation of such phenolic and alcoholic derivatives.

A summary of relationships of certain hexoses is shown in the following diagram:

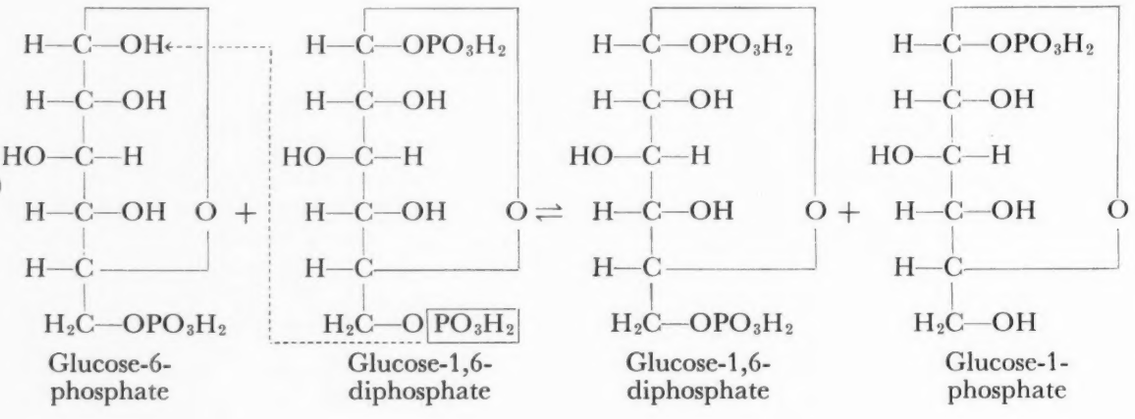


vested especially in the liver, to synthesize glucose from non-carbohydrate organic molecules. The other is the ability of various tissues to store glucose, whether of dietary or synthetic origin, as polysaccharide. This ability, very widespread in nature, results in the accumulation of starches in vegetable cells and of glycogen in animal cells.

The phenomenon of glycogen storage is a happy one in several regards. The molecule of glycogen is of enormous molecular size and of low intrinsic viscosity, hence contributes minimally to the viscous or osmotic properties of the intracellular fluid. Sugar stored as glycogen is readily available for mobilization and indeed such mobilization, and coincident deposition of hexose phosphate, occurs continuously in the normal animal. The unique source of all glycogen, so far as is known, is glucose-1-phosphate. This compound is generated in the body in an enzyme-catalyzed transphosphorylation:

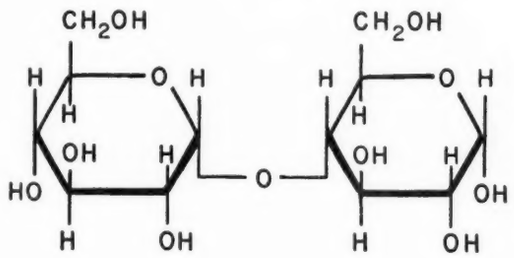
Glycogen and the Mechanism of Carbohydrate Storage. In view of the intermittent nature of ingestion of food, two devices exist in the mammalian organism to satisfy the continuous need of certain tissues, such as the central nervous system, for glucose. One of these is the capacity,

(27)

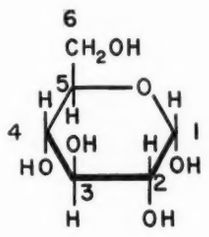


The reaction is catalyzed by the enzyme, phosphoglucomutase. Since glucose-1,6-diphosphate is both a reagent and a product of the reaction, and since its concentration does not diminish as the reaction proceeds, it need be present only in catalytic amounts. In fact, since glucose-1,6-diphosphate was a minor contaminant of impure mutase preparations, the requirement for this reagent escaped detection for many years.

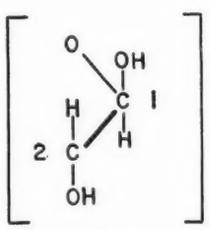
Activation of the aldehydic carbon of glucose, as by phosphorylation, appears to be a prime requisite for the biologic establishment of glucosidic bonds. A glucoside may be defined as a derivative of glucose substituted in the number 1 or aldehydic carbon atom. In the family of compounds under present discussion, the substituent is itself a glucose residue, and the parent of this family is the glucose-glucoside, maltose (XII):



With reference to the numbering of the carbon atoms of glucose drawn in this convention the oxygen bridge will be recognized as extending from carbon-1 of one glucose to carbon-4 of its neighbor:

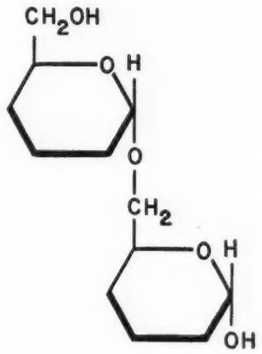


α-D-Glucopyranose

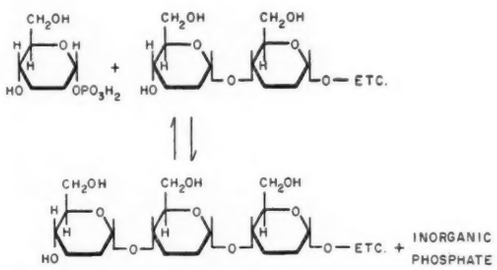


(β-D-)

The so-called α-1,4′ bond is the sole glucosidic bond of the starch, amylose. In amylopectin, and to a greater extent in glycogen, another glucosidic bond exists, the α-1,6′ bond, exemplified in isomaltose (XIII):



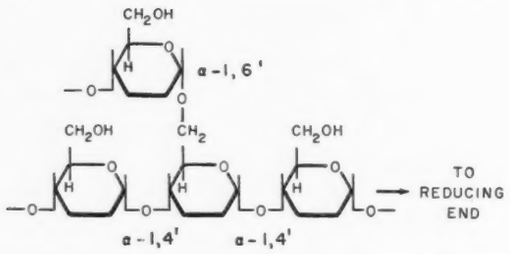
The primary step whereby the organism generates glycogen involves a phosphorolytic condensation between glucose-1-phosphate and the maltosidic end group of a pre-existing polysaccharide molecule:



(28)

This reaction is freely reversible, its equilibrium being determined by the relative concentrations of glucose-1-phosphate and inorganic phosphate. The enzyme catalyzing this reaction is phosphorylase, which has been isolated from animal as well as from vegetable sources. Under certain circumstances phosphorylase may become inactivated and then readily reactivated by addition of adenylic acid. Epinephrine favors this reactivation in the case of liver or muscle phosphorylase whereas glucagon is believed to assist in the reactivation of the liver enzyme.

The expected product of the phosphorylase reaction, generating solely α-1,4′ glucosidic bonds, would be long unbranched chains of glucose residues, each with a single reducing (aldehydic) end and a single non-reducing end. This is indeed the case with amylose. In glycogen, however, there are numerous non-reducing ends to each molecule and the molecule is highly branched. A branch point exists wherever a glucose residue bears substituents on carbon atoms 1, 4 and 6:



Phosphorylase is incapable of generating α-1,6′ bonds but a second enzyme, a "branching" enzyme, has been described which is a transglucosidase. It apparently catalyzes a reaction wherein glucose residues are transferred from α-1,4′ to α-1,6′ linkage, the new linkage being formed at the expense of the old. The enzyme has been named amylo-(1,4 → 1,6)-transglucosidase and has been shown to occur both in liver and in muscle.

The combined action of phosphorylase and the branching enzyme results in the generation of highly branched polysaccharides of an arboreal nature as shown in Figure 1. The branching patterns of liver and muscle glycogens differ somewhat, probably a consequence of difference in the relative activities of the participating enzymes. The basic scheme of polysaccharide storage is remarkably uniform throughout the animal and vegetable kingdoms.

Closely associated with the synthesis of glycogen is its enzymatic breakdown. In the gastrointestinal tract the breakdown of polysaccharides of the starch-glycogen type is initiated by the hydrolytic cleavage of α-1,4′ glucosidic bonds by the catalysis of α-amylases of the saliva and pancreatic juice. α-Amylase also exists in the blood and possibly in the solid tissues of the body but its role in intracellular glycogenolysis is obscure. Better understood is the phosphorolytic cleavage of α-1,4′ bonds, under the influence of phosphorylase, a reaction which is the precise reversal of that previously shown (reaction *28*). The attack by inorganic phosphate liberates the terminally situated glucose residue as glucose-1-phosphate. This product, by reversal of the phosphoglucomutase reaction (reaction *27*), yields glucose-6-phosphate; the glucose residue of glycogen thereby is reintroduced into the main stream of glucose metabolism.

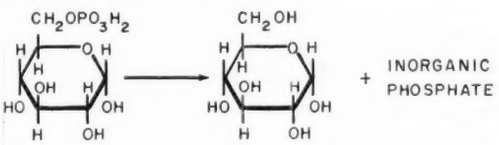
R, reducing end of molecule.
⊙, ⊖, ⊜, glucose units removed by the first, second, and third digestions with phosphorylase, respectively.
●, glucose unit split off as free glucose from 1,6 linkage by amylo-1,6-glucosidase.

FIG. 1. The structure of glycogen. (From Larner, J., Illingworth, B., Cori, G. T. and Cori, C. F. *J. Biol. Chem.*, 199: 647, 1952.

The attack by inorganic phosphate and phosphorylase upon glycogen begins at the unbranched, non-reducing ends of the glycogen molecule. (Fig. 1.) When a branch point is approached and a glucose residue in α-1,6′ linkage is exposed the action of phosphorylase ceases. This product, refractory to further attack by phosphorylase, is termed a phosphorylase limit dextrin. It can be converted into a phosphorylase-sensitive polysaccharide once again by the removal of the exposed glucose residues in α-1,6′ linkage and this is effected hydrolytically by an enzyme present in both liver and muscle, amylo-1,6-glucosidase, the "debranching" enzyme. Just as glycogenesis

from glucose-1-phosphate is a result of the combined action of phosphorylase + branching enzyme, so glycogenolysis is a consequence of the combined action of phosphorylase + debranching enzyme. Kinetic studies of glycogen turnover in the intact animal have revealed that all these processes are continuously operating in liver and in muscle. Glycogen molecules are gaining peripherally situated glucose residues (phosphorylase reaction) and at the same time new branch points are being established (branching enzyme). Since these processes occur even though the nutritional state and the glycogen content of the tissues are sensibly constant, the steps of glycogen breakdown must be pictured as accompanying those of glycogen synthesis.

A few generalizations about glycogen reserves are appropriate. In terms of weight, and more strikingly in terms of calories, the glycogen reserves of the mammal are small compared with the reserves of depot fat. The glycogen reserves of the liver are readily depleted by various procedures, including fasting, thyroid intoxication, hypoxia, etc. The glycogen stores of the muscle, although not exhausted by fasting, can be effectively eliminated by convulsions. Epinephrine administration is followed, possibly as a consequence of phosphorylase activation, by an initial depletion of glycogen. This is most obvious in the liver but in the previously fasted animal is also apparent in the muscle. Rapid breakdown of glycogen in liver may be accompanied by a rise in blood glucose due to the presence, in this organ, of a specific glucose-6-phosphatase:

(29) 

GLUCOSE-6-PHOSPHATE GLUCOSE

This enzyme is lacking in muscle, hence the only free glucose which arises when muscle glycogen breaks down is that liberated by amylo-1,6-glucosidase. Most of the biologic derivatives of muscle glycogen must by glycolyzed to pyruvic or lactic acids before they enter the blood stream.

Abnormally large accumulations of glycogen may be induced experimentally or may occur pathologically. In death due to insulin shock, enormous quantities of glycogen, especially in muscle, may be found, particularly if convulsions are avoided. Glycogen storage disease has been analyzed by Cori and in most cases its pathogenesis can be attributed to lack of glucose-6-phosphatase in liver or to abnormalities in branching pattern of the polysaccharide.

Other Polysaccharides of Biologic Importance. Dextrans, which are polyglucosides wherein the α-1,6′ linkage is the dominant one, have recently assumed practical importance in view of their use as plasma volume expanders. These polysaccharides are formed from sucrose by certain microorganisms including Leuconostoc dextranicum. The reaction involves transglucosidation by an enzyme called dextransucrase:

$$\underset{\text{(Sucrose)}}{\text{n Glucosylfructoside}} \rightarrow \underset{\text{(Dextran)}}{(\text{Glucosyl})_n} + \text{n fructose} \qquad (30)$$

A host of polysaccharides are known which, in contrast to glycogen, starch, cellulose, dextran, etc., yield more than one sugar product upon total hydrolysis. These are called heteropolysaccharides. Polysaccharides which are comprised of roughly equimolar amounts of glucuronic acid and either acetylglucosamine or acetylgalactosamine occur in connective tissues. Thus hyaluronic acid contains a repeating disaccharide unit of glucuronyl-acetylglucosamine in which the bonds are of the β-1,3′ variety. Heparin apparently has a similar structure with the additional feature of sulfuric acid residues attached along the chain. Chondroitin sulfate, the characteristic polysaccharide of cartilage, is composed of glucuronic acid, acetylgalactosamine and sulfuric acid.

The blood group substances as well as the specific soluble sugars of many bacteria belong to the class of heteropolysaccharides. Many of these have very complex structures and a variety of monosaccharides have been recovered from the products of their hydrolyses.

SUMMARY

Any attempt to separate the metabolism of carbohydrates from that of fats or of amino acids is at best arbitrary. Many metabolic pathways are now known to be shared in common between various groups of tissue constituents, many intermediates may be derived from non-carbohydrate as well as carbohydrate precursors.

In the composition of the present report the authors have limited the subject matter to the metabolic reactions of those compounds which

the organic chemist would call "sugars." On this basis, and also on the basis that it is as much a part of fatty acid or amino acid metabolism as of carbohydrate metabolism, discussion of the tricarboxylic acid cycle has not been included. An attempt has been made to review the current state of our knowledge of the origins of the common sugars, their catabolic fates, their metabolic transformations and the devices employed in their biologic storage.

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Combined Staff Clinic

Obesity

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Gilbert H. Mudge.

DR. JOHN V. TAGGART: At a time when major areas of the world face a chronically inadequate food supply it is highly significant that one of our leading nutritionists, Dr. F. J. Stare, can state that "an excessive caloric intake is the single, most extensive nutritional problem affecting public health in this country." If moderate obesity is defined as a 20 per cent excess of weight over the so-called ideal, it can be estimated that 15 million people in this country are so affected. However, to classify obesity strictly in terms of a comparison with some hypothetic ideal is undoubtedly misleading in many instances. From a medical standpoint we might better consider it as that degree of corpulence which interferes seriously with an individual's well-being or efficiency.

What are the ways in which obesity threatens the individual's well-being? Insurance statistics appear to provide tangible evidence in this matter. These have been summarized succinctly in the often repeated phrase of Louis Dublin that, "The penalty of overweight is a one-quarter to three-quarters increase in mortality." For example, in a group of persons between forty-five and fifty years of age mortality rates increase about 1 per cent for each pound excess weight. But mortality statistics alone cannot give us an adequate picture of the penalties of overweight. We know, in addition, that the obese person is more susceptible to diabetes, cardiovascular disease and cholelithiasis, that he is accident-prone and that he carries an increased risk when subjected to surgery. Perhaps even more important is the fact that excessive weight imposes a burden on day to day labor, often to the extent that work itself becomes a trial. Finally, and perhaps most serious of all, the obese individual, though he may realize no physical discomfort, may suffer most in his personal relationships.

Much of this Clinic will be devoted to a consideration of the etiologic and physiologic aspects of obesity. Let me state that we have implicit faith in the validity of the first law of thermodynamics. Many novel ways of evading this law have been proposed in the past but we must regard them as emotional and groundless. It follows, therefore, that any accumulation of tissue, adipose or otherwise, represents a positive caloric balance. The problem of obesity is largely one of balance between appetite and energy expenditure. That this balance is maintained normally by one of the most delicately poised homeostatic mechanisms merits emphasis. The majority of individuals can maintain a fairly constant weight over a period of months or years without making any conscious adjustment of their food intake to match a widely fluctuating energy expenditure. Why then are some individuals able to stabilize at an acceptable weight while others fail to do so?

First, we know that attitudes toward food vary tremendously and that these attitudes stem in part from geographic, ethnic and economic considerations. For the individual who comes from an area where food is in short supply, food becomes of tremendous importance. We know also that there are definite familial patterns of eating. The habits of eating established during childhood are perhaps among the most potent and lasting influences affecting our daily activities. Secondly, it should be noted that psychologic factors may be of paramount importance in some cases of obesity. This, too, has been aptly summarized by the late Cyril Connolly who said, "Obesity is a state of mind, a disease brought on by boredom and disappointment." While we do not wish to minimize the importance of psychologic factors in the etiology of obesity, this aspect of the problem will not be our major concern today. It is our hope that a

review of the dynamics of body weight may lead to a better understanding of the mechanisms which underlie the adjustments of appetite to metabolic needs. Our first speaker, Dr. Theodore B. Van Itallie of St. Luke's Hospital, has kindly consented to summarize for us the many important experimental contributions which have been made in this field during recent years.

DR. THEODORE B. VAN ITALLIE: For many years a large proportion of physicians and nutritionists has held that obesity is a simple matter of overeating. Like all tautologies, this thesis is logically incontestable. Yet, it evades the essential question: Why do obese persons overeat?

A decade ago, when Newburgh[1] reviewed the subject of human obesity from the physiologic standpoint, he concluded that, although many painstaking investigations had been made, no abnormal metabolic process had been disclosed to account for the accumulation of excess fat in obesity. Similarly, Conn[2] concluded that the mechanisms for dissipating energy from the obese body usually show no abnormality and that obesity must therefore result from an excessive desire for food.

The judgments of Newburgh, Conn and others that obesity in man is unaccompanied by metabolic abnormalities have tended to discourage clinical investigation into the etiology of obesity at the physiologic level; however, there have been advances in our knowledge of intermediary metabolism and in physiology and psychology which have thrown further light on the problem of obesity. As a result of the work of many investigators in these fields it is possible to set up a tentative scheme in which the various factors concerned with the regulation of food intake and fat storage may be integrated. By means of such a model it is possible to indicate some of the sites at which disorders of this "regulatory system" might be expected to occur.

A precise definition of obesity always must be arbitrary; however, Keys and Brozek[3–4] have properly emphasized that obesity in man is not necessarily determined by the simple measurement of body weight but is best demonstrated by a consideration of body composition. Nor is it completely accurate to say that all forms of obesity represent only an imbalance between energy intake and energy expenditure. This is usually the case but there are exceptions in which the body retains abnormal quantities of fat even after prolonged undernutrition.[5] Moreover, as Conn[2] has pointed out, endocrine influences may affect distribution of body fat without appreciably altering its total content.

Etiologically, there seem to be two general categories of obesity: those which are due primarily to energy imbalance, whether due to excessive intake or decreased expenditure, and those which are due primarily to abnormalities in intermediary metabolism. Such abnormalities may involve either excessive fat synthesis or impaired fat degradation. In one instance there is an excess of substrate without an accompanying metabolic disorder; in the other, there is an abnormality in the way substrates are handled by cells leading, in turn, to an increased energy intake.

TABLE 1

TENTATIVE GROUPING OF FORMS OF OBESITY ACCORDING TO MECHANISM

I. Regulatory obesity (No primary metabolic abnormality)
   - A. Psychologic
     1. Neurotic overeating
     2. Non-neurotic overeating (cultural dietary pattern)
   - B. Physiologic
     1. Increased intake—hypothalamic disorder
     2. Decreased output—forced immobilization

II. Metabolic obesity
   - A. Enzymatic—? genetic obesity in mice
   - B. Hormonal—hyperadrenocorticism
   - C. Neurologic—? lipodystrophy (autonomic)

For obesities which result primarily from disorders of energy balance without evidence of metabolic abnormality, the general term regulatory obesity might be employed. For obesities which represent primarily disorders affecting fat turnover, the term metabolic obesity seems appropriate. (Table 1.)

Regulation of Energy Intake. As a background for discussion of the various forms of obesity some sort of physiologic framework is indispensable. Although there is still a great deal to be learned about the mechanism of food intake regulation, it is known that there are two important centers concerned with hunger and satiety in the ventral hypothalamus. Each of these centers is bilaterally symmetrical, and electrolytic lesions of the more medial pair (in the ventromedial nuclei) result in hyperphagia, impaired satiety and obesity.[6] Appropriate lesions lateral to the ventromedial nuclei are followed by complete cessation of feeding. Animals with such lesions will not consume food

even if it is placed in their mouths.[7] Thus there appears to be a feeding center and a regulatory center. When the regulatory center is injured, feeding becomes uncontrolled; when the feeding center is damaged, feeding stops or is impaired. Whether the hyperphagia which follows destruction of the ventromedial nuclei results directly from interruption of some direct neural connection between the two centers or indirectly as a result of metabolic changes secondary to such destruction is not yet clear. There are autonomic and metabolic changes associated with destruction of the ventromedial nuclei which of themselves could lead to increased food intake.[8–9]

In a recent review Brobeck[10] has discussed three theories which attempt to explain the regulation of food intake. One theory proposes that animals eat for calories and that some mechanism exists for signaling the intake of a certain amount of potential energy. For example, Adolph[11] has stated that, "Food acceptance and the urge to eat in rats are found to have relatively little to do with a 'local condition of the gastrointestinal canal,' little to do with the 'organs of taste' and very much to do with quantitative deficiencies of currently metabolized materials." How the animal can measure potential energy is not known and, as Brobeck points out, no change in composition of body fluids or in pattern of intermediary metabolism directly proportional to energy intake has been identified. A recent study by Strominger, Brobeck and Cort[12] appears to exclude the caloric content as the intrinsic food factor producing the change in an animal which signals satiety.

A second possible mechanism is one proposed by Brobeck himself. His explanation is based on the fact that in the assimilation of food animals exhibit a rise in total heat production. This phenomenon has been termed by Rubner the specific dynamic action (S.D.A.). Brobeck has suggested that as extra heat is released from food it alters the conditions of regulation of body temperature and the animal stops eating to prevent hyperthermia. Thus, according to Brobeck, animals "eat to keep warm."

In support of Brobeck's hypothesis is the finding of Booth and Strang[13] that the rise in skin temperature after eating has the same course in time as that of the S.D.A. and correlates well with the onset of satiety. Moreover, when the composition of the diet is changed to alter the concentration of protein, carbohydrate, fat, or the total bulk, rats will adjust their intake so that the calculated S.D.A. varies less than any other known factor of the diet.[14] And, of course, it is well known that the hypothalamus contains temperature-sensitive cells.

The "thermostatic" theory described by Brobeck has several questionable features. For example, the mechanisms ordinarily employed by the body to dispose of extra heat and to maintain temperature are so effective that it seems superfluous to invoke hunger and satiety as additional thermoregulatory devices. There is no evidence to suggest that hot food *per se* has a greater satiety value than the same amount of food served cold, or that a hot bath destroys one's appetite. It is evident that energy is needed for the performance of work as well as for the maintenance of body temperature. Hence the concept of "eating to keep warm" appears to neglect the fact that any theory of food intake must account for the conditioning effect of changing energy requirements upon energy intake. No relationship has been identified between S.D.A. and energy requirements.

A third theory of food intake listed by Brobeck is the "glucostatic" theory of Mayer and his associates.[15–17] Briefly, this theory postulates that satiety occurs during active uptake of blood glucose by appropriate receptors in the central nervous system and that the desire for food is felt only when the supply of blood glucose to the "glucoreceptors" is curtailed. Thus, from the glucostatic view, the quantity of carbohydrate available in the body at any one time exerts a regulatory effect on food intake.

Brobeck's major criticism of the glucostatic theory has been that the existence of glucoreceptors in the central nervous system is unproved.[10] Actually, there is little doubt that such glucoreceptors exist. Duner[18] has recently demonstrated that there is a center in the hypothalamus sensitive to changes in local concentration of glucose. When the glucose concentration in the hypothalamic region is selectively elevated inhibition of epinephrine secretion by the adrenal medulla follows. This effect is mediated via the splanchnic nerves. A number of investigators have shown that lowering the blood sugar by means of insulin stimulates gastric peristalsis.[19] If the vagi are sectioned this effect is abolished. Conversely, raising the blood glucose level may result in inhibition of gastric peristalsis,[20–21] although

intravenous administration of amino acids does not appear to affect the motility of the stomach in fasting dogs.[22] Hence it seems probable that there are centers in the hypothalamus responsive to changes in blood glucose and capable of initiating and inhibiting gastric contractions, and of influencing the rate of epinephrine secretion by the adrenal.

Larsson (and Forssberg)[23] recently reported studies on the metabolism of the hypothalamic region which contains centers known to be concerned with the regulation of food intake. They measured radiophosphate incorporation and the hydrolyzable phosphate content (creatine phosphate and energy-rich terminal groups of adenosine triphosphate) in three hypothalamic areas (A, B and C) of fed and fasted rats. Their analyses disclosed that in the area of the hypothalamus containing the lateral and ventromedial nuclei (C) significantly more P^{32} was taken up in hungry than in fed animals. The others, control (A and B) areas, of the hypothalamus did not display such increased phosphate retention during hunger and, indeed, showed less P^{32} uptake in the fasted than in the fed state. The livers of hungry rats were distinguished by an increased uptake of radiophosphate; however, blood, muscle and cerebrum as a whole showed no significant differences in phosphate incorporation when the fasting and fed states were compared from this standpoint. The concentration of energy-rich phosphate was markedly higher in the C-samples than in the control hypothalamic areas of hungry rats. The opposite was found in fed rats.

These findings are consistent with the view[16] that the hypothalamic areas concerned with food intake may be more characteristic of peripheral cells in their metabolic properties than they are of brain tissue. For example, if they behaved like nervous tissue in their uptake of glucose they would be unable to signal impending depletion of available carbohydrate since nervous tissue uses carbohydrate at a more or less constant rate regardless of whether the organism is starved or fed.[24]

Peripheral arteriovenous glucose differences appear to serve as better indexes of the availability of blood glucose to body tissues than either arterial or venous levels alone.[16] Large arteriovenous glucose differences, properly interpreted, correlate well with satiety; however, further confirmatory studies are needed before it can be stated with assurance that such an association has etiologic significance. A correlation also has been described between small arteriovenous glucose differences and desire for food. (Fig. 1.)[21]

The hypothalamus is connected by neural pathways to the cerebral cortex; there are also efferent fibers which travel from the hypothalamus to the gastrointestinal tract. A connection exists between the hypothalamus and the fat depots: the sympathetic nerves, which innervate adipose tissue, link with neurons originating in the hypothalamus.[25] If the hypothalamus is visualized as subject to influences from the cerebral cortex as well as from the circulating blood and sensory nerves from the periphery, the importance of so-called psychosomatic factors in the scheme of food intake regulation becomes intelligible. Stunkard[26] has shown that talk about food with patients cannot elicit gastric hunger contractions if active utilization of carbohydrate (as inferred from peripheral arteriovenous glucose differences) is taking place. Gastric hunger contractions can be elicited if peripheral arteriovenous glucose differences are small. On the other hand, certain emotionally disturbed patients, notably schizophrenics, will deny that they are hungry even when powerful gastric contractions are being recorded on the kymograph. Thus it would appear that physiologic and psychologic factors relating to food intake may interact at the diencephalic level, each exerting a modifying influence on the other.

Energy Expenditure. Energy balance is a matter of energy expenditure as well as of energy intake. Hence it is appropriate to mention briefly the role of activity in the genesis or prevention of obesity. Mayer[27] has shown that there is an enormous difference in spontaneous activity between hereditarily obese mice and non-obese control groups. The obese animals are practically inactive. However, this inactivity is not the result of extreme obesity but precedes it, as is shown by comparison of activity rates of non-obese animals and young pre-obese mice of the same weight.

Thus it is possible to ascribe to this decrease in activity a role in etiology of the obesity which develops somewhat later. Indeed, from a thermodynamic standpoint the rate of fat accumulation of mature hereditarily obese mice is inexplicable unless the role of activity is taken into account. When hereditarily obese mice carry the "waltzing" gene and are in constant

rotary movement in their cages, they rarely gain excessive weight.

It has always been assumed that in normal animals food intake bears a constant relationship to activity. Although this is true within the normal "physiologic" limits of activity, there are situations in which activity is so great that food intake lags behind and the subject concerned loses weight. A recent study has shown that, conversely, when activity is quite low, food intake tends to level off and will remain constant even while activity progressively decreases.[28] The result in this instance, of course, is weight gain. (Fig. 2.)

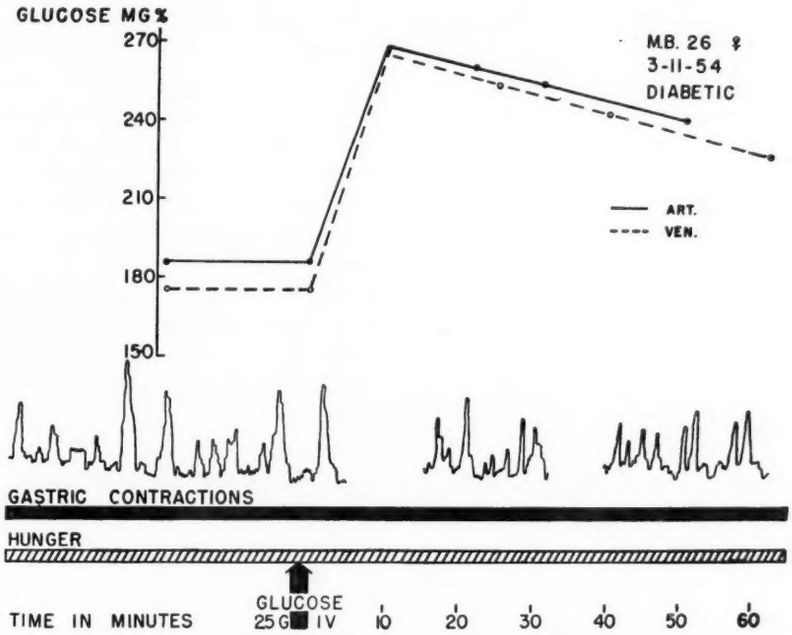

FIG. 1. Failure of intravenously administered glucose to abolish gastric hunger contractions in a patient with uncontrolled diabetes mellitus (Stunkard and Wolff[21]).

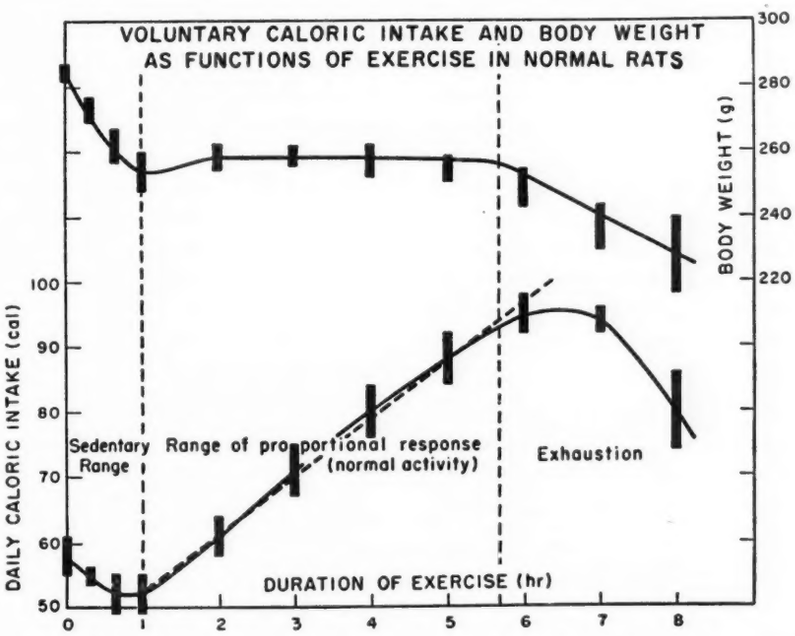

FIG. 2. Food intake and body weight as functions of duration of exercise in normal adult rats (Mayer et al.[28]).

These observations suggest that in man an increasingly sedentary existence may not be accompanied by a proportionate decrease in food intake. It is possible that the slowly progressing mild obesity of middle age may be explained on this basis.

Factors Influencing Fat Synthesis and Degradation. Metabolic obesity is considered to be primarily determined by the rate at which fat is formed or broken down. Of course, since injury to certain "regulatory" hypothalamic centers may affect metabolism, it is difficult to classify that form of experimental obesity in which injury to the hypothalamus is followed by a mixture of regulatory and metabolic abnormalities.[8–9]

Fat deposition and mobilization are under three forms of control acting synergistically, namely, enzymatic, hormonal and nervous. (It is worth being reminded that hormones do not initiate events within cells but merely regulate the rate at which some of the events occur.)

A major factor favoring fat mobilization and oxidation is lack of insulin. In diabetes mellitus and in the "diabetes" of carbohydrate starvation lipogenesis is greatly decreased and lipolysis is greatly accelerated. In order for glycolysis to continue, glucose must be able to enter cells. This it apparently cannot do readily without an effective supply of insulin. Moreover, the process of lipogenesis from 2-carbon fragments appears to depend upon glycolysis in that the energy needed for lipogenesis must be derived from the glycolytic process.[29]

Both in tissue slices and in intact animals it has been shown that the oxidation of longer chain fatty acids is strikingly influenced by carbohydrate. Geyer[30] has shown that fasting accelerates the oxidation of palmitic acid by rat liver slices. Pyruvate added to the medium decreases significantly the palmitate oxidation by such slices. In the intact rat oxidation of palmitic acid and tripalmitin is increased by prior fasting of the animal and decreased by prior glucose administration.[31]

Cellular carbohydrate deficiency also is associated with increased secretion of hormonal factors which are believed to stimulate fat mobilization. A pituitary substance may act to increase the rate of lipolysis; how this is accomplished is not clear.[32] The adrenal cortex also influences fat mobilization, apparently by playing a "permissive" role.[33] It has also been reported that epinephrine secretion and the integrity of the sympathetic nervous system are needed for effective mobilization of fat stores.[34–35]

When an adequate supply of insulin is available to the organism, lipogenesis is not inhibited and may increase if an "excess" of glucose is transferred into cells. Adipose tissue itself can synthesize fat. Shapiro and associates[36] have reported that adipose tissue *in vitro* will take up fatty acids from serum. Hausberger *et al.*[37] have compared the relative abilities of liver and of adipose tissue to form fat by measuring rates of conversion of radioactive glucose to fatty acids and carbon dioxide by both tissues. They demonstrated in normal animals that radioactive glucose is utilized for lipogenesis and is oxidized by liver and adipose tissue. By contrast, liver and adipose tissue of alloxan-diabetic rats are incapable of converting glucose carbon into fatty acids. Of particular interest is their finding that insulin administration *in vivo* restored hepatic and adipose tissue lipogenesis to normal levels and that continuation of insulin treatment promoted high levels of lipogenesis in both tissues. Administration of insulin to the alloxan-diabetic rats not only accelerated glucose metabolism to carbon dioxide and fat but also altered the channeling of energy so that much more fat was produced.

When we speak of adipose tissue as being more or less metabolically inert it is because we do not take into account the large mass of triglyceride usually stored in the depots. If the large difference between lipid and protein content in liver and adipose tissue is taken into account it can be demonstrated that adipose tissue is far more active than liver both in oxidizing glucose and in converting glucose to fat.[37] An excess of insulin has a more marked effect on lipogenesis in both tissues than upon glucose oxidation. Incidentally, the fact that more triglyceride is stored in the body in obesity does not mean that there is a larger amount of active adipose tissue. Hence the ability of the obese person to convert carbohydrate to fat should not be enhanced just because the quantity of fat stored in the adipose tissue is great.

According to Levin and Farber[33] adrenalectomy will greatly inhibit or prevent the fat mobilization which otherwise follows fasting, anterior pituitary extract administration or exposure to the appropriate stress. (Adrenalectomy also inhibits fat deposition.) If mice subjected to adrenalectomy are pre-treated with cortisone they can again mobilize their fat

in response to such trigger factors as APE, growth hormones and stress.

Hausberger[38] has shown that when the nerve connections supplying the symmetric interscapular fat body of the mouse are cut on one side only, an influx of glycogen and, in its wake, an accumulation of fat can be observed within ten hours after denervation. The fat content of the denervated side exceeds that of the control side in the normally fed as well as in the starved mouse. The denervated side can be depleted of fat only after long periods of hunger. As Wertheimer and Shapiro[39] point out in their excellent review, normal innervation seems a requisite for the attainment of a dynamic equilibrium in fat tissue.

It appears, then, that the factors which favor lipogenesis are usually those which also favor entry of glucose into cells. Presumably, insulin acts to increase lipogenesis by accelerating transfer of glucose into cells and not by an effect within the cell. By contrast, factors which act to exclude glucose from cells favor increasing fat mobilization and oxidation.

Relation of Abnormalities in Fat Metabolism to Regulation of Energy Balance. In order to relate abnormalities in synthesis and metabolism of fat to an over-all imbalance of energy intake and energy expenditure, a mechanism capable of mediating between energy expenditure and food intake must be considered. Although such a regulator has not been delineated in a quantitative sense it appears that the concept of a "glucostatic" mechanism permits the gap to be bridged between an apparently primary disorder in fat metabolism and an associated disorder of energy balance. This postulated relationship is indicated in Figure 3.

Ordinarily carbohydrate and fat both serve as fuels for energy expenditure in a proportion presumably determined by the amount of carbohydrate available to peripheral cells. When, for example, the blood sugar falls to fasting levels or below, homeostatic mechanisms come into play which cut down drastically on the rate of peripheral glucose utilization, stimulate gluconeogenesis from protein, decrease lipogenesis and stimulate fat mobilization from the depots. Under such circumstances increasing amounts of fat are metabolized.

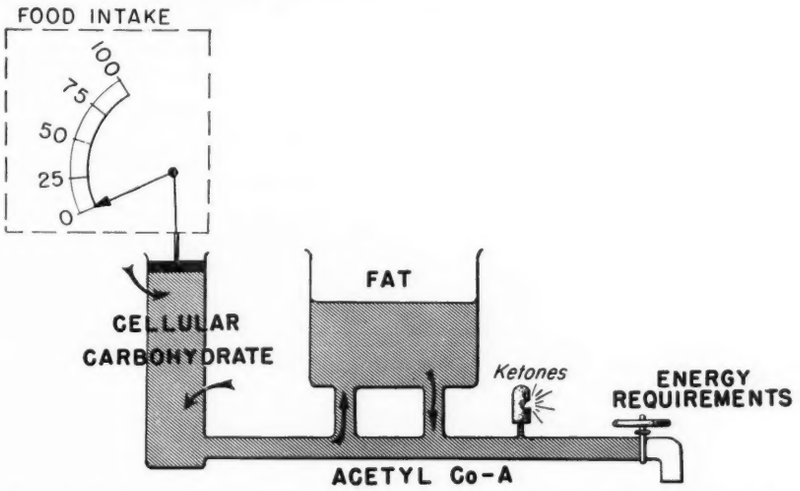

FIG. 3. Postulated relationship between energy requirements, cellular carbohydrate supply and food intake.

According to the glucostatic theory desire for food is also a part of the complex homeostatic activity designed to protect the organism, notably the central nervous system, against carbohydrate privation. In theory, if available carbohydrate were shunted too rapidly to fat or if the fat depots were unable to contribute their share of energy to metabolism, carbohydrate would be depleted at an abnormally rapid rate and food intake and fat stores would increase. In diabetic-like states food intake is frequently increased but, since lipogenesis is impaired under such circumstances, fat is lost rather than gained. Naturally, when energy requirements are increased, as in exercise or hyperthyroidism, spontaneous food intake usually increases proportionately. However, in such instances lipogenesis is curtailed somewhat and fat is readily utilized.

Adolph,[11] writing of the mechanism which

governs the urge to eat, states that "the investigator gains the feeling that some complex of internal compositions intermittently drives the animal to eat so that some resultant concentration is kept just above or below a threshold value." The supply of carbohydrate within the cell seems to correspond well to Adolph's postulated "complex of internal compositions." The supply of cellular carbohydrate depends upon the availability of blood glucose, and blood glucose is readily available to non-nervous cells only during periods of relative hyperglycemia. Such intervals of hyperglycemia, in turn, ordinarily occur only after meals. A relationship between the rate carbohydrate is utilized and the energy requirements of the body has not been worked out. However, the rate of carbohydrate utilization seems to correspond better to the rate of energy expenditure than does the degree of S.D.A. obtained after a meal. Such a glucostatic theory explains better than the thermostatic theory the hyperphagia associated with uncontrolled diabetes mellitus, hyperthyroidism and treatment with corticotropin and cortisone.[6] Finally, since maintenance of a certain minimal glucose level is absolutely indispensable to life, the body would be expected to ensure regular replenishment of its supply of carbohydrate from outside sources.

TABLE II

"CLINICAL" COMPARISON OF THREE FORMS OF EXPERIMENTAL OBESITY

Variety of Obesity	Hereditary Obesity-Diabetes Syndrome (mouse)	Gold-Thioglucose-Induced Obesity (mouse)	Hypothalamic Obesity (rat)
Origin	Recessive mendelian entity	Injection of LD_{50} of gold thioglucose	Electrolytic lesions of ventromedial nuclei
Adjustment to dietary dilution	Relatively normal	Abnormal	Abnormal
Spontaneous activity	Markedly diminished	Normal	?Normal
Oxygen consumption	In proportion to lean body mass, not body surface	Follows surface law (splanchnomegaly occurs with obesity)	Normal
Resistance to cold	Poor	Normal	Normal
Response to insulin	Insulin resistant	Normal	Sometimes insulin sensitive
Response to growth hormone	Marked hyperglycemia in response to growth hormone injection	Normal	Normal
Blood glucose level (non-fasted)	Hyperglycemic after 8th week	Normal	Lower than in controls
Endocrine anatomy	Increase in number and size of pancreatic islets	Normal	Gonadal atrophy, renal lesions
Response to high fat diet	Loses weight	Obesity accelerated	Obesity accelerated

If the normal relationship between energy requirements and cellular carbohydrate supply were disturbed by an appropriate metabolic disorder, it should be possible according to the glucostatic hypothesis, to predict that obesity will occur. A consideration of certain recent metabolic studies made on obese animals may serve to illustrate the prediction value of this hypothesis.

Experimental Obesity. Three forms of experimental obesity have been carefully studied, hypothalamic obesity,[6,17] gold thioglucose obesity[40–41] and the hereditary obesity-hyperglycemia syndrome in mice.[42–43] These forms of experimental obesity cannot be discussed in detail in this presentation but certain of their clinical characteristics are compared in Table II.

It is of particular interest, however, to determine whether or not these forms of obesity can be understood in terms of some disordered mechanism or mechanisms. One of the first questions that might be asked about these three forms of obesity is whether they differ in terms of body composition. Bates and coworkers[44] have shown that the iodine and saponification numbers of the triglycerides synthesized by the three groups of animals are similar to those of their non-obese controls. The total cholesterol content of the hereditarily obese animals is higher than it is in their controls. All of the obese animals display an increase in liver weight and, of course, in total fat content.

When incorporation of labeled acetate into fatty acids is determined in the three forms of experimental obesity the metabolic differences between them are more clearly defined.[45] For example, hereditarily obese mice with slight caloric deficit retain much more dietary acetate as carcass fatty acids than do their sibling controls. When hypothalamic hyperphagic rats and genetically obese mice are fed one-half the number of calories previously found necessary to maintain caloric equilibrium, they retain significantly more C^{14} from dietary radioacetate in carcass fat than do their controls. Gold thioglucose obese mice in negative caloric balance retain the same amount of C^{14} from labeled acetate as do their controls. Since the specific activity in the fat of the obese animals is the same as that in their controls, the increased retention of the label observed in the hyperphagic rats and genetically obese mice cannot be regarded as a dilution phenomenon.

The fact that there is a relatively increased retention of C^{14} from radioacetate during negative caloric balance in the hypothalamic rat suggests that the operation has produced a profound alteration in the metabolic pattern. It is also of unusual interest that the genetically obese mice continue to synthesize fat at an appreciable rate even during caloric restriction, a circumstance associated with drastic diminution of lipogenesis from acetate in normal animals. Such findings are consistent with the observations of Alonso and Maren[5] that genetically obese mice underfed for six months, so that their body weight was 30 per cent less than that of their non-obese siblings, still contained several times as much fat as their controls.

Bates, Mayer and Nauss[46] also have studied fatty acid turnover in the three forms of obesity under consideration. Radioactive carboxyl labeled palmitic acid was used as the tracer and the average amount of fat mobilized during the experimental period was calculated by measuring the decline in isotope content of carcass fat with time. If the means of the amount of fat mobilized daily are assumed to be fairly accurate, it is possible to calculate the per cent of fat gain that is due to decreased mobilization and that due to increased synthesis (Table III). Such calculations suggest that the fat accumulated by the gold thioglucose-obese animals can be accounted for to some extent by decreased mobilization, while the fat accumulated by the obese-hyperglycemic mice appears to result about equally from decreased mobilization and increased synthesis. The hypothalamic rats show a remarkable decrease in fat mobilization.

TABLE III
CALCULATED ORIGIN OF INCREASED FAT CONTENT IN THREE FORMS OF EXPERIMENTAL OBESITY*

Rates	O-H Obese Mice	G.T.G. Obese Mice	Hypothalamic Rats
Expected rate of fat Accumulation per day (g)	.13	.18	1.12
Actual rate (g)	.27	.18	1.76
Synthesis rate (per cent of control)	152	100	154
Mobilization rate (per cent of control)	56	60	5

* Bates, Mayer and Nauss.[46]

It is worth pointing out that one of the strong arguments against the "lipophilia" explanation of obesity has been the fact that adipose tissue cells of obese persons do not appear to resist mobilization of fat during undernutrition. A number of nitrogen balance studies have indicated that obese persons utilize their own fat as readily as do non-obese individuals.[2] For this reason it would be premature to interpret human obesity in terms of the metabolic behavior of experimentally obese animals. Nevertheless, these preliminary observations on fat metabolism in three forms of experimental obesity appear to illustrate several of the postulated metabolic disorders which it was predicted could result in obesity.

To summarize, an attempt has been made to view obesity as an end product for which a number of disorders, each affecting energy balance in its own way, might be responsible. A tentative classification of "obesities" in terms of etiologic mechanisms is proposed. Such disorders appear to fall into two broad categories, those affecting primarily the regulation of energy balance (regulatory obesity), and those affecting primarily the intermediary metabolism of foodstuffs and fat turnover, and secondarily energy balance (metabolic obesity).

It is believed that the "glucostatic" theory of food intake regulation is of considerable heuristic value in approaching the vast, complex problem of human and experimental obesity. Although this theory cannot be regarded as established at the present time, it appears to account more satisfactorily than other contending formulations for the cyclic nature of hunger and satiety on the one hand and the conditioning effect of energy requirements upon the urge to eat on the other.

Lastly, metabolic studies on fat metabolism in three forms of experimental obesity have been described in support of the view that the etiology of obesity can be multiple and that the unitary concept of obesity in man as a simple matter of overeating requires critical re-examination.

DR. TAGGART: We should like to turn our attention now to certain of the basic principles in the clinical management of obesity. I know of no more challenging problem for the practitioner of medicine. Our writer, Cyril Connolly, has said that, "Imprisoned in every fat man a thin one is wildly signalling to be let out." Unfortunately, when the obese patient is confronted with a suitable regimen for weight reduction, the thin man inside too often begins to signal less and less frantically. I hope that Dr. Sidney Werner will tell us, if he can, how this problem can be managed least painfully.

DR. SIDNEY C. WERNER: The success of the long-term treatment of obesity is apt to be slight. Nevertheless, the results often are enough to encourage further efforts. Any treatment must follow the usual principles either of trying to attack the cause of the disorder or of rectifying, if possible, some resulting physiologic abnormality. This discussion will not include those situations in which an evident physiologic disorder is the cause of obesity, such as hyperadrenocorticism, adenoma of the pancreas and hypothalamic injuries.

Some years ago Dr. Hilde Bruch, at the Babies Hospital in New York, became interested in the problem of the etiology of obesity and was especially struck by the parental relationship that existed between the mother and the obese child which, she concluded, led to the child's overeating. In short, the increase in appetite was based not upon a need for food but upon the fact that the child responded to emotional upset by eating. In the majority of obese people observed at the clinic it was believed that this emotional origin was more often the cause of their overeating than was any physical defect. There are many pathways by which emotional overflow can result in an increased appetite.

Dietary restriction, that is decreasing caloric intake in relation to caloric output, has been the fundamental principle behind therapy for obesity. The work of Dr. Newburgh many years ago showed clearly that reduction in caloric intake below the body's needs inevitably leads to weight loss. Unfortunately, upon the institution of starvation (which is what such caloric reduction really means) there is a corresponding reduction in the rate of basal metabolism. With reduction to levels as low as −30 per cent, what was originally a low calorie diet may soon become a maintenance one.

It is also well to bear in mind that certain small individuals have basal metabolism requirements which are not much greater than 1,200 or 1,400 calories, so that 1,200 calories may be far from a low calorie diet. Most people like to feel satisfied after having eaten. A low caloric diet does not have a large bulk so that those placed on such a regimen are likely to feel disturbed and hungry.

Attempts have been made to tackle the problem of weight reduction by increasing heat loss. High protein diets have been used for this purpose on the assumption that specific dynamic action can be increased and hence the patient can be made to expend more energy. It can be said from personal experience with several patients in the metabolism ward that the amount of weight loss produced by a 200 gm. protein diet is insignificant, and I do not feel that this regimen is a very successful one.

The use of a high fat diet has also been recommended by Pennington. The theory was partly suggested to him by the work of Mayer and his associates, and held as its essential principle that fat introduced into the metabolic mixture will

be burned without being involved in the metabolism of glucose. This hypothesis is open to criticism since it is almost certain that excess of fat can cause fat deposition without the need of fat entering the Krebs cycle. However, the practical fact is that when one administers a high fat diet, some patients lose weight. This has been borne out in our experience and, of course, one wonders why. Have the laws of thermodynamics been disproved?

If fat was burned and not utilized for anabolism, a large heat output from the body with a high fat diet could explain how a patient would fail to gain or would actually lose weight. However, the work of Newburgh many years ago showed clearly that, although obese people do have an increased heat output, it is not out of proportion to their increased body mass. Thus there is no evidence that obese people eliminate excess heat indicating excessive catabolism of fat.

In order to pursue further the question of why some people lose on a high fat diet containing as much as 2,800 calories, patients were admitted to the metabolism ward for study. I will show the results and some of the difficulties in such a study.

The first patient showed an abrupt loss in weight when placed on the diet originated by Dr. Pennington. He then lost less weight on an isocaloric high carbohydrate diet and had another drop in weight on a second trial of the Pennington regimen. Unfortunately, however, this patient developed diarrhea on the high fat diet.

The second patient maintained weight with the high fat diet, then increased her weight on the standard diet. However, it is well known that in the shift from a high fat to a high carbohydrate diet there is retention of salt and water. Thus it became evident that fluid, sodium and potassium balances had to be determined in order to give meaning to the experiment.

This was done with a third patient who showed a slight decline in weight under the influence of the Pennington regimen. There was sufficient shift in her sodium and water balance to make it seem likely that that was all that was happening.

Similarly, a fourth patient developed slight weight loss on the high fat regimen, accounted for largely as loss of salt and water. I should mention that the last two patients, who had been amenorrheic for at least six months or a year, started menstruating two days after the baseline diet period was completed and the Pennington diet begun. As you know, salt and water are retained just before menstruation and are subsequently lost.

The last two patients show clearly what happens with a 2,800 calorie high fat, low carbohydrate diet and with a diet of isocaloric content high in carbohydrate and low in fat. In these two men there was virtually no difference in the loss of weight between the two diets.

To discuss a different type of approach, the use of a low salt diet in dietotherapy has been recommended. Essentially, I think, its value lies only in decreasing the palatability of the diet.

Still another approach has been the effort to influence appetite adversely. The analeptic agents, such as benzedrine® and dexedrine,® have been used. It is probable that these agents are effective but they soon lose their efficacy and, at a time of emotional upset, they are little protection against the urge to eat.

Just as glucose given intravenously decreases appetite, amino acids, particularly glutamic acid, given intravenously have a very potent anorexigenic action. For that reason a series of products containing amino acids for oral use have appeared on the market. We were asked to appraise one of these products and set up an experiment in which there were three regimens: (1) the particular preparation with added amino acid; (2) a placebo; and (3) adhering only to the instructions accompanying the preparation advising the patient to limit diet, eat lettuce, bulky foods, and so on. It was interesting to see that by following the last regimen the patients lost somewhat more than with either the placebo or the amino acid preparation in question.

Finally, several preparations have been introduced which are designed to dull the sense of taste. As Dr. Van Itallie has just pointed out, these are not very rewarding.

Attempts to provide psychotherapy, when an emotional derangement is the cause of the obesity, suffer from several handicaps. For one, there appears to be an age limit beyond which psychotherapy has little value. In fact Dr. Richardson at the New York Hospital made a careful psychoanalytic survey of several patients and concluded that after a certain age the protection provided by the obesity is so necessary to the individual that it is dangerous to attempt psychotherapy or too vigorous weight reduction.

At any rate, intensive psychotherapy is not economically feasible for most people. However, mild psychotherapy through the patient's own doctor is extremely valuable and is readily available. The fact that a doctor sees an obese patient and doesn't look repelled or disappointed is often in itself psychotherapeutic. These obese people who are somewhat dependent often do better in the hands of a sympathetic physician than when consulting one who has no interest in the problem.

There are several drugs designed to stimulate the basal metabolic rate which should be mentioned. Dinitrophenol we all know to be so toxic that its use can never be recommended. As for the use of thyroid gland preparations, many studies have shown that unless toxic doses are used the patient's own thyroid gland has a remarkable capacity to decrease its function in proportion to the amount of thyroid administered. Thus very little is accomplished except for a week or two.

Exercise is of little avail in weight reduction since the human body can do considerable work on a small amount of food. To reduce weight by exercise in the way Dr. Van Itallie's rats did leads ultimately, as it did in them, to exhaustion. Moreover, many people after exercise eat more than enough to make up for the calories expended in this way.

Massage is even more futile and there is no evidence that increasing local circulation in this way mobilizes fat depots.

DR. TAGGART: Thank you, Dr. Werner. That completes the formal part of the program. We have allowed time for discussion, and I am happy to see that we have with us this morning Dr. Hilde Bruch and Dr. Albert J. Stunkard.

There was one point in therapy which was not mentioned and concerning which I think Dr. Van Itallie has some information, that is, the use of hydrophilic colloids.

DR. VAN ITALLIE: We have recently completed a clinical study involving comparison of the anorexigenic effects of a hydrophilic colloid preparation and a preparation containing amphetamine. Approximately sixty obese patients who are being observed in our Nutrition Clinic served as subjects. Alternate patients received tablets identical in appearance to be taken three times per day before meals. One tablet contained 200 mg. of carboxymethylcellulose, the other 200 mg. of carboxymethylcellulose plus 10 mg. of amphetamine. In all other respects the patients were treated in the same way.

For the first six weeks the patients given the preparation containing amphetamine lost an average of 0.77 lb./week. For the entire thirty-week period of study the same group (which diminished in number as well as in weight as time passed) lost an average of 0.55 lb./week. The patients on colloid alone lost an average of 0.15 lb./week for the first six weeks. For the entire thirty weeks their weight loss averaged 0.10 lb./week. The differences between the means of the two groups were statistically significant. Moreover, when another group of patients was switched from the colloid to the tablet containing amphetamine without their knowledge a statistically significant increase in weight loss followed. Another control series of thirty-five patients who had been seen in the clinic on another occasion and who had received no medication lost slightly less weight on the average than the group treated with amphetamine (0.43 lb./week over a thirty-six week period).

These results indicate that the colloid preparation in the quantities prescribed was of no value and may have interfered with the reducing regimen by providing the patient with something he thought was a crutch. By contrast the amphetamine seemed to have a definite anorexigenic effect, particularly during the first six weeks of therapy. However, the results obtained in the second control group receiving no medication at all suggest that amphetamine is of limited value in the management of obesity. It is no substitute for sympathetic supervision by the physician but it may be temporarily helpful if used in conjunction with such supervision.

MR. FRED KATZ: Why does basal metabolism go down during fasting?

DR. WERNER: That is an interesting question. Efforts to study thyroid function under conditions of starvation suggest that the thyroid remains more or less intact. However, it is quite interesting that corticosterone in thyroidectomized patients will increase the metabolic rate quite sharply. There is a recent paper about a growth hormone describing a non-specific increase in the metabolic rate not mediated through the thyroid. If one developed an adaptation to starvation through the adrenal or the pituitary, one could quite readily have an extrathyroid decrease in metabolic rate.

MR. BYRON HARDIN: Is there any evidence

that thyroid substance could overcome the effect of that decreased rate?

DR. WERNER: Well, not so far.

MR. PETER ROWLEY: Querido claimed that in two groups of rats on isocaloric diets, one group getting all their food at one time and the other having it spread throughout the day, different rates of fat accumulation resulted. The group receiving the single massive meal showed a definite gain of weight over those who received the food over the course of the day. Is that true?

DR. WERNER: That is quite true. Perhaps it is a matter of specific dynamic action. There is evidence to indicate that the flare-up three times daily in specific dynamic action is greater than that with the same amount of food given in a single meal. Is that your impression, Dr. Van Itallie?

DR. VAN ITALLIE: I think that is partly the explanation. Brobeck and Tepperman were able to demonstrate a similar rapid rate of fat accumulation when they were trying to explain the remarkably high respiratory quotients exhibited by hypothalamic animals after ingestion of food. They fed normal rats a full day's ration within a two-hour period and observed that animals trained to eat in this manner developed an extraordinary ability to convert ingested carbohydrate and, presumably, protein to fat. I assume that these particular animals converted an equivalent quantity of fat into energy later in the day. However, had they been allowed to eat another meal some hours hence, obesity might well have ensued.

DR. TAGGART: Quantitatively, how important a factor is specific dynamic action?

DR. WERNER: I think it is about 6 to 10 per cent of the energy requirement.

DR. VAN ITALLIE: Protein alone is about 10 per cent. The lower figure occurs with a mixed diet.

DR. TAGGART: I was surprised to hear the thermostatic theory revived. Is this not really another version of the old "luxuskonsumption" advocated many years ago, namely, that heat production could increase, *pari passu*, with caloric intake? I thought Newburgh answered that when he told of putting an individual on a 3,500 calorie diet with a resultant heat production of some 2,900 calories per day. When the caloric intake was increased to 5,000 calories a day, heat production went from 2,900 to about 3,000 calories.

DR. R. J. CROSS: May I ask about the glucostatic theory? It was suggested that the level of glucose within the cells might be responsible for appetite. I have wondered if it might not be some breakdown product of glucose rather than glucose itself, pyruvate, for example, or something of that sort.

DR. VAN ITALLIE: The only evidence I know of is the previously cited work of Larsson and Forssberge. You will recall that they demonstrated a preferential uptake of radiophosphate by hypothalamic tissue in the area of the "feeding" center when the rats under study fasted. We know that phosphate enters cells with glucose in many instances; therefore, the supply of phosphate to the cell might be crucial. I think that whatever the crucial reaction is, whether it involves some breakdown product of glucose, high energy phosphate bonds, intracellular potassium or something else, the proponents of the glucostatic theory tie it to the carbohydrate supply. Thus the availability of carbohydrate to the postulated glucoreceptor is seen as the limiting factor regardless of the events which take place after the glucose has entered the receptor cell. All this, of course, is highly theoretical and speculative.

DR. TAGGART: Dr. Bruch, I would like to ask you a loaded question. We have devoted most of our time today to a consideration of physiologic and biochemical factors which may operate in the deposition and mobilization of fat. Would you care to tell us how important you believe these factors to be in comparison with the psychological factors which operate in a great many cases?

DR. HILDE BRUCH: You certainly are loading the question by putting it as an either/or proposition. I think the psychological factors are terribly important. Their historical development is of interest. In my first studies on obesity I reviewed the literature and ran across all the different ideas. I felt that they made sense for a psychosomatic approach but that we did not have sufficient data on the metabolic aspects. Therefore, my answer to your question is that the basic physiologic facts are so important that I can think of no better way of progressing in this problem.

But these discoveries have nothing to do with the answer to the second part of your question. The psychological problems are also important. It is fairer in our approach to patients not to deal with these problems as mutually exclusive.

Dr. Van Itallie separated them as two different forms in his classification. According to my way of thinking, they are interrelated and are not two separate problems.

The best part of the new work will be its application to the management of obesity. This new knowledge lifts the approach out of the realm of the ridiculing, the moralizing and the condemning that has so often characterized the attitude toward fat people. It permits a more positive approach to these patients so that they will be treated with the respect they deserve.

DR. ROBERT F. LOEB: Is it fair to say, regardless of what group of factors play what relative roles, that we still have to reduce the number of calories (1) below the patient's appetite and (2) to a point where he actually loses weight? From the point of view of the physician, I think the most important thing in the management of these patients is to let them know that we know it is as difficult for them to reduce their caloric intake to the point of negative nitrogen balance as it would be for the rest of us who are not obese to go on a starvation regimen month in and month out, year in and year out. If this is brought to the attention of the patient I think we are doing a great deal toward helping him with his own problem. He must be helped.

DR. BRUCH: I would go one step further and raise the fundamental question of whether it is really good medicine to approach the weight problem directly. Again, I refer to follow-up studies. I have seen many patients who, if the weight they had lost over twenty years was added up, should have disappeared; yet there they are very much in existence. All this effort, self-restraint and self-denial are completely wasted. It seems that many fat young people go back to their previous weight (or a bit higher) after efforts at reducing. This is in agreement with the observations that have been made on starvation. If after a starvation experiment the body has gained complete restitution, the drive for excess eating persists for some time. It seems to me that Dr. Loeb's approach is the correct one. One should let the patient know that he will react to starvation like any normal person. This is one clue to the puzzle that many fat people, after an unjustified reducing regimen, will become even heavier. They react exactly like normal people after starvation. They continue overeating.

DR. ALBERT J. STUNKARD: There is another question I would like to ask in regard to the selection of patients who are dieting. An occasional patient is observed who, if placed on a diet, becomes seriously disturbed or psychotic. I wonder if Dr. Bruch might make some remarks in regard to the selection of patients?

DR. BRUCH: That is the point Dr. Werner mentioned, that Dr. Richardson had made certain observations on the development of neurotic symptoms in fat people. Dr. Richardson studied patients who were somewhat advanced in years. My observations have been made chiefly on adolescents, and it seems to me that they as a group are even more fragile in their total adjustment. When one approaches their problem by forcing them to lose weight, they are apt to develop serious mental symptoms. The fact that they are fat suggests that their life adjustment was poor at the start. They have been persecuted for being too heavy and feel rejected as people. The weight becomes an issue in a precarious mental balance. Enforced reducing is an attack on their security and may lead to psychotic reaction, that is, to a frank schizophrenic episode. In this group of patients I have also seen benzedrine addiction or, more correctly, something that has a delusional character. It is unlike addiction in which a patient feels physiologically tied to a drug. The delusional aspect is the conviction that "without these pills, I cannot function any more."

SUMMARY

DR. GILBERT H. MUDGE: Obesity is a condition which constitutes a serious public health problem because of the frequency and severity of its associated complications. In today's clinic, obesity has been considered in terms of physiological and biochemical mechanisms as well as in terms of the therapeutic procedures available to the clinician.

The physiological mechanisms may be divided into those primarily associated with total energy balance of the organism and those primarily related to disturbances of intermediary metabolism. The problem of food intake has been discussed in terms of the control of appetite by discrete functions of the central nervous system. The prevailing theories of the physiological basis of satiety have been reviewed. Hypothalamic centers, which are probably sensitive to glucose or other related metabolites, have been described. The function of these

centers has been analyzed in terms of the glucostatic theory of appetite control.

The metabolism of fat is regulated by enzymatic, hormonal and neural factors, and these are briefly reviewed. Adipose tissue itself has been found to have a surprisingly active metabolism. Three types of experimental obesity are discussed in terms of disturbances of specific metabolic reactions. These demonstrate the possibility that, from a metabolic point of view, obesity may be considered in terms of multiple etiologic factors.

In considering the various forms of therapy it is concluded that dietary restriction of caloric intake must still be considered the major component of any therapeutic program for obese persons. Psychiatric factors are frequently found to be responsible for the discrepancy between appetite and energy expenditure which results in clinical obesity. It is therefore emphasized that the advisability of weight reduction must be carefully evaluated in relation to the emotional problems presented by each individual patient.

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Clinico-pathologic Conference

Right-sided Heart Failure Occurring during Successive Pregnancies, Polycythemia and Sudden Peripheral Vascular Collapse

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THIS twenty-seven year old white housewife (No. 237929) was admitted to the Barnes Hospital on two occasions in the four months prior to her death. Her first admission was on May 27, 1954.

The patient had been in good health until twenty-four months before admission when she noted mild dyspnea on exertion during the third month of her second pregnancy. Shortly thereafter her ankles became swollen to a mild degree. These symptoms did not progress, however, and she had no further difficulty before or after delivery. Six months later she developed the same symptoms of dyspnea and ankle edema during the fourth month of her third pregnancy. Subsequently she became easily fatigued, gained weight slowly, and was delivered of a premature infant after seven months' gestation.

Her general health improved slightly after delivery until six months before the next admission, when she consulted her physician because of a recurrence of ankle edema. She was told that she had a "goiter" and an "enlarged heart." She was treated with digitalis and Lugol's solution, 15 drops per day, which resulted in moderate improvement. Four months before admission she discontinued the medications without consulting her physician. One month later she began to experience attacks of palpitation due to the sudden onset of rapid heart action followed by an abrupt disappearance of this symptom. Three months before admission her legs became progressively larger, eventually becoming swollen above the knees. During this time she was moderately dyspneic but not orthopneic. Two weeks before admission her abdomen became markedly swollen, and she again consulted her physician. At this time she was redigitalized, placed on a low salt diet and given intravenous injections which resulted in rapid loss of the edema. A week before admission she noticed that her fingernails had become a dark blue, and she complained of a "tight feeling" in her chest. She was immediately hospitalized and given oxygen which resulted in subsequent clearing of the cyanosis. While in the hospital she was again given Lugol's solution, 10 drops per day. When after five days she failed to improve she was transferred to the Barnes Hospital.

The past history revealed that the patient had been the product of a normal delivery. There had been no cyanosis at birth, no known congenital defects, nor any unusual or severe disease during childhood and adolescence. Seven years before admission she had consulted a physician because of dysmenorrhea which was ascribed to a "tilted womb." At that time she was told that she had an "enlarged heart" and "palpitation of the heart," although she had not noticed any cardiorespiratory symptoms. The condition of the patient's mother, age sixty-three, had recently been diagnosed as "rheumatic heart disease." One sister had had a "toxic goiter" removed at Barnes Hospital.

The personal and social history were not contributory.

Physical examination at the time of admission revealed the patient's temperature to be 37.6°C.; respirations, 16; pulse, 120, and blood pressure 98/68. She weighed 84 pounds. The patient was a well developed, small, chronically

ill white woman in no acute distress. The skin was warm and slightly moist and there was no evidence of cyanosis. There was no significant lymphadenopathy. An acute chalazion of the right upper eyelid with erythema, swelling and tenderness, especially of the lateral portion, was noted. No proptosis of the eye or drooping of the lid was encountered. The optic fundi were normal. Further examination of the head and neck revealed only an asymmetrical goiter with the left lobe and isthmus enlarged to twice normal size. The lungs were not remarkable. Examination of the heart revealed a point of maximum impulse in the fifth intercostal space at the mid-clavicular line. On percussion the left border of cardiac dullness was encountered at the anterior axillary line. The cardiac rate was rapid; the rhythm was regular. A protodiastolic gallop rhythm was heard over the cardiac apex. A grade 1, low pitched murmur was heard in middle and late diastole over the cardiac apex in the anterior axillary line, and a soft grade 1 systolic murmur was noted along the left sternal border. The first heart sound at the cardiac apex was not accentuated. The second heart sound over the pulmonic area was increased in intensity. Examination of the abdomen revealed no abnormalities except for a firm liver edge palpable two fingerbreadths below the right costal margin. Only a trace of ankle edema was present. Results of the neurologic examination were within normal limits.

The laboratory data were as follows: hemoglobin, 20 gm. per cent; red blood cells, 6,500,000; white blood cells, 8,500; differential, normal. Urinalysis, specific gravity, 1.017; pH 5.0; protein, 1 plus; sugar, negative results; centrifuged sediment: 8 to 10 white blood cells and 1 to 3 red blood cells per high power field. Stool guaiac test gave negative results. Blood cardiolipin, negative results. Blood chemistry: non-protein nitrogen, 27 mg. per cent; total proteins, 7.0 gm. per cent; albumin, 4.0 gm. per cent; sodium, 145.9 mEq./L.; potassium, 4.7 mEq./L.; carbon dioxide combining power, 24.2 mM/L.; protein-bound iodine, 11.4 μg. per cent. Electrocardiogram: right ventricular enlargement; sinus tachycardia; auricular enlargement; digitalis effect. Roentgenogram of the chest: cardiac enlargement, left auricular and right ventricular; pectus deformity. Venous pressure, 240 mm. of saline. Antistreptolysin "0" titre, 250 units. C-reactive protein, 3 plus. Throat culture: moderate growth alpha streptococci; few pneumococci. Blood culture, no growth. Basal metabolic rate, −3 per cent.

The patient's course in the hospital was uneventful. A therapeutic regimen was maintained consisting of a low salt diet and digitalis leaf in maintenance dosage by mouth. She remained afebrile and free of respiratory distress. The chalazion of the right eye responded promptly to the local application of bacitracin ointment. During hospitalization many cardiopulmonary diagnoses were suggested. On June 7, 1954 the patient was subjected to cardiac catheterization. The results were as follows:

Source	Blood Oxygen Content (vol. %)	Blood Oxygen Saturation (%)	Pressure (mm. Hg)
Pulmonary artery	11.96	57.3	80/45
Right ventricle (high)	12.77	61.2	80/0
Right ventricle (low)	11.82	56.8	
Right auricle	11.84	56.9	
Superior vena cava	10.99	52.5	

Pulmonary capillary pressure was 9 mm. of mercury. Simultaneous arterial oxygen saturations from the brachial and femoral arteries each yielded values of 98 per cent. The results of these studies were interpreted as follows: "Mitral stenosis is very unlikely. There is pulmonary hypertension. There is no evidence of a left to right shunt." The patient was discharged on June 15, 1954.

On September 16, 1954 the patient was brought to the emergency room in extremis. She had been seen a week before in the cardiac clinic and seemed to be doing well. Her polycythemia was again noted, and plans had been made to rehospitalize her soon to study the cause of the increased red cell production. The day before admission it was noted that her face and neck had begun to swell. Shortly thereafter she became nauseated, complained of palpitation, vomited, and retched frequently. She became very apprehensive and quite restless. She was taken to her local physician who advised that she be brought immediately to this hospital.

Physical examination on admission revealed her temperature to be 37.0°C., respirations, 30, and pulse, 130. The blood pressure reading was unobtainable. The patient appeared very ill and was obtunded. The skin was ashen gray in color,

cool and moist. The lips were cyanotic. The head and neck revealed no change from the previous examination except for the neck veins, which were distended. The lungs were not remarkable. Examination of the heart revealed a forceful point of maximum impulse just to the left of the mid-clavicular line. The cardiac rhythm was regular, and a protodiastolic gallop rhythm was heard at the cardiac apex. No peripheral arterial pulsations were palpated except over the femoral arteries bilaterally. The edge of the liver was palpable four finger-breadths below the right costal margin. A mild degree of pitting edema of the thighs and sacrum was present. Neurologic examination was not remarkable.

The laboratory data were as follows: hemoglobin, 18.5 gm. per cent; white blood cells, 13,950; differential: stabs 6 per cent; segmented forms, 83 per cent; lymphocytes, 8 per cent; monocytes, 3 per cent. The electrocardiogram revealed no change from the previous record.

Within two hours after arrival in the emergency room the patient expired. During that period she remained dyspneic, restless, cyanotic, and in a state of vascular collapse.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case today is one that excited a good deal of interest on the wards. The patient was a young woman of twenty-seven. Past history was non-contributory. She began to suffer from signs of cardiac decompensation during her second pregnancy twenty-four months before her death. She recovered from this with the birth of her child. The third pregnancy came some six months after the second and was again characterized by cardiac failure. After the delivery of her premature child she recovered partially but the last six months of her life were made miserable by progressive cardiac failure. The one noteworthy aspect of her history is that at the age of twenty, during an incidental illness, she was told that her heart was large, although she had no symptoms. Furthermore, in the last year or two of her life a goiter was discovered. Presumably it was a toxic goiter for which she was given Lugol's solution. On her first admission the physical signs, aside from the goiter, were entirely referable to her cardiac embarrassment. She exhibited a high venous pressure, accentuated pulmonary second sound, an enlarged right ventricle by x-ray, and electrocardiographic evidence of enlargement of the right auricle. She was not cyanotic, which is an important observation. The only significant laboratory observation was a considerably increased red blood cell count. She became compensated during this first admission and did well for the three months after she returned home. She then came in again and died rather suddenly. Now may we see the x-ray films?

DR. WILLIAM B. SEAMAN: Conventional x-rays of the chest were taken on the day following hospital admission. A deformity of the thoracic cage and a depression of the sternum, the so-called pectus deformity, were noted, which is important to consider in evaluating the cardiac size because the thoracic cage deformity does tend to displace and rotate the heart, complicating the problem of chamber analysis when cardiac enlargement exists. The heart was obviously enlarged, the apex extending to the sixth anterior interspace a few centimeters lateral to the left mid-clavicular line. Usually this is considered to be evidence of left ventricular enlargement; however, there was definite right ventricular enlargement. In the presence of enlargement of the right ventricle it is difficult to determine radiographically whether there is left ventricular enlargement as well. Films made during barium swallow did not present very good evidence for left auricular enlargement. Prominence in the region of the main trunk of the pulmonary artery was also noted, suggesting that this artery may have been a little dilated. The lung fields were of particular interest in this case since the vessels were certainly normal in size, perhaps even a little less than normal. We had no radiographic evidence of pulmonary hypertension, even though it was present clinically. It is true that we have had cases of true pulmonary hypertension in which the vessels were not large; the explanation for this I do not know. There was also a film taken at the time of cardiac catheterization which suggested a tremendous enlargement of the right ventricular cavity, thus tending to confirm our impression of the conventional films.

DR. ALEXANDER: There are two points, Dr. Seaman, that puzzled us. It was very difficult, without being somewhat extravagant with our imagination, to understand why the left auricle was enlarged. Do you think that we may forget about that?

DR. SEAMAN: I personally do not feel that it was enlarged.

DR. ALEXANDER: Secondly, we were puzzled over the fact that the pulmonary conus was not appreciably enlarged.

DR. SEAMAN: Most of the films suggest that there was pulmonary artery dilatation. On the other hand, a very similar bulge in that area can result from right ventricular enlargement alone.

DR. ALEXANDER: Did the infundibulum of the conus appear enlarged?

DR. SEAMAN: We couldn't see that because it was the portion just beneath the valve.

DR. ALEXANDER: On the basis of the clinical findings, the suggested diagnoses were mitral stenosis or some form of congenital heart disease, more likely Eisenmenger's complex. Would you comment on these, Dr. Massie?

DR. EDWARD MASSIE: The first diagnosis that would have to be entertained clinically on this patient would be mitral stenosis if the auscultatory findings are correctly listed in the protocol. This would comprise the diastolic murmur at the apex, the accentuated pulmonic second sound and the enlarged right ventricle. Those add up to mitral stenosis, but wasn't some murmur heard at the left sternal border or at the pulmonary area? Were the murmurs in this patient heard only at the apex?

DR. ALEXANDER: Everyone who observed the patient heard a murmur along the left sternal border that was systolic in time, but not diastolic.

DR. MASSIE: We do know that in a septal defect, either auricular or ventricular, we would be likely to get some auscultatory finding at the left sternal border. Now, admittedly, in an interauricular septal defect sometimes one has a paucity of findings, but with a ventricular septal defect we ought to get a loud systolic murmur of some sort at the left sternal border. This patient did not have such a murmur, so it is unlikely that an interventricular defect was present. I also feel that mitral stenosis would have been the most likely diagnosis clinically prior to the findings obtained at catheterization.

DR. ALEXANDER: Dr. Bercu, I think my remarks will not be nearly as valuable as yours in the discussion of this situation. You wrote a note on the chart which stated that this was probably not mitral stenosis because the pulmonary capillary pressure was normal. Dr. Massie felt that in the absence of a louder murmur than was heard at the left sternal border an interventricular defect was unlikely. Did you feel that you had ruled this out by catheterization?

DR. B. BERCU: It is impossible to rule out septal defect with certainty when the pressure on the right side of the heart rises abnormally. Depending upon the pressure differential between the two ventricles and the size of the defect, one can miss a small defect with a left to right shunt, or a larger defect as the pressure on the right side rises and the shunt reverses, so that probably many cases in the literature cited as primary pulmonary hypertension really are septal defects without enough shunt to be obvious on catheterization. There is one other technic in using the catheter that might be worth mentioning. Unfortunately, we were not employing it at that time. It consists of injecting dye into the area of the shunt and measuring the time it takes for it to appear in a peripheral artery. Had we done that at the time we could have been more certain.

DR. ALEXANDER: You said that you did not think there was a left to right shunt. Why?

DR. BERCU: I did not think so because the oxygen content of the blood samples taken from the right side of the heart showed no significant rise as we went from the superior vena cava to the pulmonary artery. All the values were normal.

DR. ALEXANDER: If there were a left to right shunt would there have been more oxygenation of the right ventricular blood?

DR. BERCU: Yes.

DR. ALEXANDER: Pulmonary stenosis was suggested as a possible diagnosis here. How may catheterization rule this out?

DR. BERCU: That is the easiest diagnosis to rule out by catheterization, because if the systolic pressure in the pulmonary artery is equal to that in the right ventricle there is no doubt that pulmonary stenosis is absent. In the presence of pulmonary stenosis, the pressure in the pulmonary artery is markedly diminished as compared to that of the right ventricle.

DR. MASSIE: Since what you said rules out pulmonary stenosis, what about pulmonary insufficiency on the basis of the catheterization data?

DR. BERCU: You're probably thinking of the wide pulse pressure, Dr. Massie, which suggests that diagnosis. It is impossible to be certain about the presence of pulmonary insufficiency. In the presence of this type of pressure recording and of a high-pitched diastolic murmur heard along the left sternal border, which this patient

did not have, I would be willing to make a diagnosis of pulmonary insufficiency.

DR. MASSIE: In other words, your readings would be compatible with pulmonary insufficiency.

DR. BERCU: Yes.

DR. ALEXANDER: Would you get a loud P_2 in pulmonary insufficiency?

DR. BERCU: In the absence of pulmonary stenosis, yes, because the pulmonary insufficiency must be secondary to pulmonary hypertension.

DR. ALEXANDER: What is the mechanism of the murmur?

DR. BERCU: The valves probably close with a loud bang, but there is just enough space between them for some blood to leak back.

DR. ALEXANDER: Any other question?

DR. JOHN R. SMITH: Is the diastolic pressure of 45 mm. Hg in the pulmonary artery compatible with a wide-open pulmonary insufficiency?

DR. BERCU: I was speaking of the usual pulmonary insufficiency, which is a functional lesion secondary to pulmonary hypertension and dynamically probably not too important. If you are speaking in terms of dynamics and the effect on the right ventricle, I would agree with you that a high diastolic pressure in the pulmonary artery would be unlikely in pulmonary insufficiency.

DR. JAMES W. OWEN: The important thing is that neither a septal lesion nor a pulmonary insufficiency can explain the primary pathology here, which was right-sided hypertension.

DR. BERCU: That is not entirely true. Although a septal defect *per se* does not cause right-sided hypertension, about 10 per cent of those patients with either an auricular or a ventricular septal defect ultimately develop severe pulmonary hypertension. We also know that in the Eisenmenger complex pulmonary hypertension is a part of the lesion, so that diagnosis should have been considered.

DR. ALEXANDER: The absence of any definite lesion of the heart, the valves or the septum that may have accounted for this picture led to the consideration that the resistance might be in the pulmonary artery, and so a suggestion was made that this might be primary or perhaps secondary pulmonary artery hypertension. I believe, Dr. Wood, you made that diagnosis before the catheterization studies were done. I wonder if you'd tell us your concept of primary pulmonary artery hypertension.

DR. W. BARRY WOOD, JR.: Dr. Alexander, I suggested that diagnosis because I couldn't see the left auricular enlargement in the x-ray films. In addition, the patient had had trouble at the time of her pregnancy, which suggested the possibility of thrombi in the pulmonary circuit. Since all our evidence pointed to right-sided heart strain and pulmonary hypertension, it seemed to me that she might be suffering from a block in the lesser circulation, that is, in the pulmonary vessels, which was throwing a strain on the right ventricle, causing the very loud second pulmonic sound, and leading to her symptoms.

DR. ALEXANDER: The block, then, would be proximal to the pulmonary capillaries?

DR. WOOD: Yes, and the fact that the pulmonary arteries at the hilar region were not enlarged, as Dr. Seaman pointed out, raises the question as to whether the thrombi might not have been fairly close to the pulmonary conus involving the large pulmonary arteries.

DR. ALEXANDER: I am not very clear as to whether you are now speaking of so-called primary pulmonary hypertension or whether you feel there will be thrombi or a lesion somewhere in the lungs.

DR. WOOD: I was thinking in terms of multiple pulmonary thrombi leading to pulmonary hypertension. In those cases that I know about, the pathologist can demonstrate changes in the pulmonary blood vessels, either marked sclerosis of the small pulmonary arteries or thrombi that have become recanalized. There must be something producing a block, either in terms of sclerosis of the vessel walls or thrombotic changes inside the vessels. Those are the only changes with which I am familiar.

DR. ALEXANDER: This would be analagous, then, to systemic hypertension.

DR. WOOD: In a sense, yes.

DR. ALEXANDER: Dr. Owen, you're interested in this subject. Do you agree with this suggestion?

DR. JAMES W. OWEN: Yes, Dr. Alexander. As a matter of fact an increasing number of these cases is being discovered now that cardiac catheterization is being done with increased frequency, and both mechanisms Dr. Wood has described have been offered to explain various cases. It is interesting that studies of the pathology of the lung show that most of the changes have been limited to vessels having a diameter of 100 micra or greater. In the differential diagnosis it is important to distinguish this kind of cor

pulmonale from that secondary to chronic lung disease. Fortunately this woman is certainly one of a small number of women who have trouble during pregnancy and run a rapidly fatal course with progressive signs of cor pulmonale. The other interesting features that these patients almost uniformly demonstrate are the absence of orthopnea and the presence early in the course of their illness of normal oxygenation of arterial blood.

DR. ALEXANDER: In my earlier medical experience, this diagnosis meant that nothing was found at autopsy. Later on, more careful study of these cases did reveal minute healed thrombi or other larger thrombi. When we speak of primary pulmonary hypertension, we might be aware of the fact that this isn't necessarily primary. Dr. Bercu, how did you interpret her polycythemia?

DR. BERCU: I had great difficulty interpreting it, Dr. Alexander, for this reason: On two occasions we did determinations of her arterial oxygen content and saturation; in both of those instances we found that the arterial oxygen data were perfectly normal. Our usual concept of secondary polycythemia is that it occurs on the basis of anoxia or hypoxia, with a diminished arterial oxygen concentration and conceivably a diminished oxygen concentration in the bone marrow. If this is so, this patient did not have secondary polycythemia. On the other hand, the fact that pulmonary disease is often associated with pulmonary hypertension and with polycythemia would lead one to call this a secondary polycythemia. It is conceivable that she had primary polycythemia, but I would think this very unlikely.

DR. ALEXANDER: May we assume that the lesion is not in the pulmonary capillaries? If this were early Ayerza's disease, wouldn't the pulmonary capillary pressures be raised even in the earlier stages?

DR. BERCU: I am not sure of that. It is my impression that pulmonary capillary pressure would not be elevated unless there was disease of the left ventricle or the mitral valve.

DR. ALEXANDER: But if there were thrombi or fibrosis in the pulmonary capillaries, shouldn't one see eventually some evidence in the chest x-rays and shouldn't the capillary pressure be increased?

DR. BERCU: Changes could have taken place in the alveolar walls which would have nothing to do with the blood vessels, such as the interstitial change we see in an alveolar-capillary block which does not elevate capillary pressures. I'm not aware of any studies which show rises in the pulmonary capillary pressure from changes in the pulmonary capillaries themselves.

DR. ALEXANDER: Are there further questions about this case or shall we decide that, in all probability, this is a case of disease of the pulmonary artery itself? We are still a little uncertain about the polycythemia. Dr. Massie, do you agree with this?

DR. MASSIE: I am somewhat skeptical about the primary pulmonary vascular disease. I'm sure this patient didn't have mitral stenosis. Since we have ruled out that possibility, I wonder whether pulmonary insufficiency might have produced this type of polycythemia. I'm puzzled that we did not see more pulmonary vascular markings; this makes me hesitate to make a diagnosis of pulmonary insufficiency.

DR. ALEXANDER: You have made a very good point. Certainly in many of the cases that have been described, one of the features is a prominent pulmonary conus. Are there other questions or suggestions?

DR. MASSIE: I should say one thing about the electrocardiogram. There is no question that it showed marked right ventricular enlargement; we also made an electrocardiographic diagnosis of auricular enlargement, but it must be remembered that with pulmonary hypertension that kind of electrical pattern does appear, which does not necessarily require anatomic enlargement of the auricle. I agree that there was no left auricular enlargement on the x-ray films.

A PHYSICIAN: It is not safe to say there was no enlargement of the pulmonary conus. As Dr. Seaman pointed out, it is entirely probable that there may have been, especially on the right anterior oblique film. I would be inclined to say that the pathologist will tell us there is enlargement of the pulmonary conus.

DR. OWEN: Dr. Alexander, in regard to the polycythemia, I think it's worth mentioning that this is not a constant finding in this disease.

DR. ALEXANDER: We will turn this discussion over to the pathologists with a clinical diagnosis of primary pulmonary hypertension.

PATHOLOGIC DISCUSSION

DR. JOHN D. KEYE: The pleural cavities contained 250 ml. of a clear serous fluid in each hemithorax. The heart was markedly enlarged with dilatation of the right ventricle and atrium

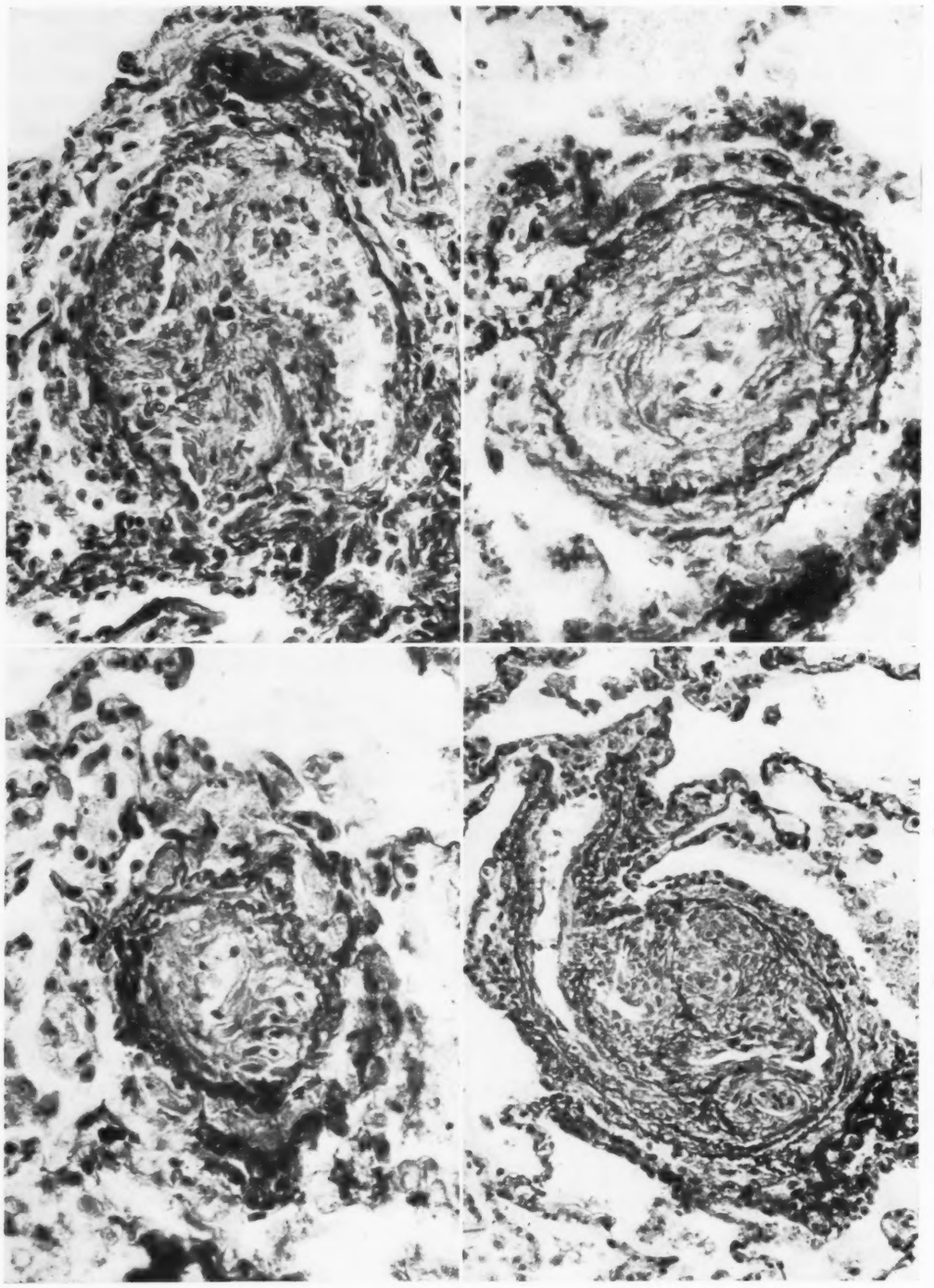

Fig. 1. Fibrous tissue and endothelial channels typical of an organized thrombus in a small pulmonary artery. This is one of two types of occlusive lesions that were present in tremendous numbers in the vessels of the lungs.

Fig. 2. Concentric fibrous intimal thickening in a small muscular artery (the second type of occlusive lesion of pulmonary arteries in this case).

Fig. 3. A lesion of the second type in an arteriole.

Fig. 4. Irregular intimal fibrous thickening in a terminal branch of an arteriole which suggests in its appearance a form intermediate between the obvious organized thrombi and the concentric lesions which are usually considered as arteriosclerotic.

and hypertrophy of their walls. The left ventricle and atrium were of more nearly normal configuration. The pulmonary valve, as well as all the other valves, was normal. The myocardium was not remarkable except for hypertrophy and the endocardium was thin and transparent. The thyroid was palpable but weighed only 24 gm.; upon section it did not appear unusual. The lungs were moderately edematous and congested. The large pulmonary arteries contained a few yellow plaques in the intima. The appearance of the liver was typical of advanced chronic passive congestion, and there was congestion of the spleen and of the kidneys. The veins of the legs, unfortunately, were not examined.

DR. WILBUR A. THOMAS: On microscopic examination all of the abdominal organs showed evidence of long standing congestive failure. Such changes were especially prominent in the liver, spleen and pancreas. The thyroid showed a few dilated acini but there was no evidence of increased activity. The lungs contained a few areas of a slight degree of congestion and edema, but there was no evidence of significant pulmonary fibrosis or emphysema. The significant pathologic changes in the lungs were limited to the small arteries and arterioles. Examination of these small vessels makes it apparent that the cause of the pulmonary hypertension in this patient was multiple obstructive lesions at this level.

These obstructive lesions were of two types. In the small pulmonary artery illustrated in Figure 1, it consists of a meshwork of loose connective tissue through which are scattered endothelial-line vascular channels. This is the usual and easily recognizable appearance of an organized thrombus, and on the left side of the figure it can be seen to bulge into a branch of the vessel. Figure 2 is an example of the second type of lesion, which consists of fibrous intimal thickening. This is a small muscular artery with a clearly defined muscular wall and internal elastica. The intima within the elastica is thickened by loose fibrous tissue that encroaches upon the lumen in a rather uniform fashion to reduce its size greatly. Figure 3 shows a similar lesion, this time in an arteriole. There are marked fibrous intimal thickening and a very small lumen. The lesion in Figure 4 is somewhat less advanced and considerably more irregular. It is in a terminal branch of a small muscular artery at the origin of an arteriole and its appearance suggests an intermediate stage between the first and second types of lesions. It is impossible to estimate the extent of these lesions. It is quite probable that there were literally millions of them. It can be readily appreciated that the degree of obstruction produced by large numbers of these lesions would be sufficient to result in pulmonary hypertension and eventually in right heart failure.

Our problem is to determine the basic nature of these lesions and, if possible, their etiology. Until very recent years, as Dr. Alexander pointed out, cases such as this probably would have been classified in most clinics and laboratories as primary pulmonary arteriosclerosis or Ayerza's syndrome. Ayerza's syndrome is a rather loosely defined term usually indicating any type of pulmonary arterial disease the cause of which is not immediately apparent. Considerable evidence has been acquired in recent years indicating that many of the cases previously called by this name are actually cases of latent pulmonary embolization with the lesions in pulmonary vessels resulting from repeated showers of small emboli. The evidence for this viewpoint comes from three sources, namely, animal experiments, autopsy observations and clinical observations. This is a very good example of the results that can be achieved with this combined approach.

Seven years ago a British pathologist, C. V. Harrison,[1] had a case similar to the present one. It occurred to him that these lesions might be due to emboli. In order to test this idea, he embolized a group of young, healthy rabbits by repeatedly injecting a saline suspension of blood clots into a peripheral vein and allowing them to be carried by the blood stream to the lungs. By means of this simple method, he was able to produce lesions like those seen in his human case and in the case being discussed here. His results have been confirmed by investigators in other laboratories throughout the world and we have duplicated them in some recent experiments of our own. Reports of animal experiments such as those by Wartman and others,[2] and Barnard,[3] as well as that of Harrison

[1] HARRISON, C. V. Experimental pulmonary arteriosclerosis. *J. Path. & Bact.*, 60: 289, 1948.

[2] WARTMAN, W. B., JENNINGS, R. B. and HUDSON, B. Experimental arterial disease: the reaction of the pulmonary artery to minute emboli of blood clot. *Circulation*, 4: 747, 1951.

[3] BARNARD, P. J. Pulmonary arteriosclerosis and cor pulmonale due to recurrent thromboembolism. *Circulation*, 10: 343, 1954.

include photomicrographs of lesions that are indistinguishable from the two types shown in the present case. The second type of lesion, the fibrous intimal thickening, may or may not necessarily be another form of organization of thrombi. It may be due to the hypertension that has been produced by the obstruction from lesions of the first type, which are easily recognized as organized thrombi. In any event, both types of lesions are readily produced by injecting emboli of blood clots into experimental animals.

In recent years, increasing numbers of human cases have been reported with pulmonary vascular lesions similar to those in the present case and associated with clearly demonstrable sources of emboli in the veins of the legs or the right portion of the heart. Several years ago we studied the autopsies of twelve such cases at the Massachusetts General Hospital.[4] Lesions of both types, recanalized thrombi and typical arteriosclerosis, were constantly present in the arteries of the lungs. In nine of these twelve cases there were clearly demonstrable sources in the leg veins or heart, usually in the leg veins, from which emboli could have arisen. In two cases the leg veins had not been examined because of failure to recognize their importance at the time of autopsy. In only one case no source of emboli was found despite a complete examination.

Supporting evidence for this concept of the etiologic importance of pulmonary emboli in these cases comes from clinical observations. Careful histories have revealed in some cases, although by no means in all, episodes which were suggestive of embolization. A number of cases have also been reported with onset dating from pregnancy, a condition of which thrombotic and embolic episodes have long been recognized as complications.

In summary, this is a case of chronic cor pulmonale resulting from multiple obstructive lesions in the small pulmonary arteries and arterioles. Evidence has been derived from experimental animals, autopsies and clinical observations indicating that these lesions may have resulted from multiple emboli. The source of emboli in this case was not demonstrated, but the veins of the legs, which are the most common source, were not examined because of failure to recognize the possibility at the time of the autopsy that they might have been important in clarifying the pulmonary condition. The immediate cause of death was not apparent, but in a number of the previously studied cases the terminal episode has also been rather sudden.

Final Anatomic Diagnoses: Multiple organized thrombi in the small pulmonary arteries and arterioles; slight arteriosclerosis of large pulmonary arteries and advanced arteriosclerosis of small pulmonary arteries and arterioles; myocardial hypertrophy and dilatation of the right ventricle and atrium.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

[4] Owen, W. R., Thomas, W. A., Castleman, B. and Bland, E. F. Unrecognized emboli to the lungs with subsequent cor pulmonale. *New England J. Med.*, 249: 919, 1953.

Research Society Abstracts

Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE ANNUAL MEETING, NEW ORLEANS, LOUISIANA, JANUARY 29, 1955

PHYSIOLOGIC VARIATIONS DURING INDUCED HYPOTHERMIA IN THE DOG. *H. M. Ausherman, W. K. Nowill, S. Boyarsky, H. E. Hall and W. W. Shingleton (introduced by J. V. Warren*).* Dept. of Anesthesia, V. A. Hospital, Div. of Anesthesia and Urology and the Dept. of Surgery, Duke University Hospital and School of Medicine, Durham, N. C.

Recent enthusiasm for the use of induced hypothermia for cardiac surgery and the hibernation technic for severe infection and other shock-like states prompted the authors to familiarize themselves with the technics and physiologic variations of induced hypothermia in the dog. Hypothermia was produced most rapidly and efficiently by emersion in ice water under pentothal® or nembutal® sodium anesthesia. Biologic functions tested were as follows: blood pressure, pulse rate and electrocardiographic changes, respiratory rate, tidal and minute volume, oxygen consumption, electroencephalographic patterns, serum potassium and sodium, arterial pH, carbon dioxide tension, per cent oxygen saturation, hematocrit, renal and hepatic functions.

Respiratory rate, minute volume and oxygen consumption are markedly depressed. Arterial carbon dioxide pressure and pH vary toward respiratory alkalosis. Arterial blood remains well oxygenated until respiration is nearly absent. Serum sodium was essentially unchanged but serum potassium was decreased. Blood pressure and pulse rate declined progressively with the decrease in rectal temperature. Electrocardiographic changes were those associated with a sinus bradycardia and alkalosis.

Hypothermia in the dog appears to be a relatively safe procedure at body temperatures at or above 25°C. and for less than twelve hours. Temperatures below 25°C. and for more than twelve hours have a progressively higher mortality.

* Asterisks indicate members.

DACTIL (N-ETHYL-3 PIPERIDYL-DIPHENYL-ACETATE HYDROCHLORIDE) IN TREATMENT OF VENTRICULAR ARRHYTHMIA INDUCED BY OUABAIN. *D. P. Baumann and L. D. Seager (introduced by P. L. Day*).* Univ. of Arkansas School of Medicine, Little Rock, Ark.

Recent attempts to find an effective antifibrillary agent for use in the arrhythmia of hypothermia has led to the trial of many drugs with indifferent results. Studies with dactil® (Lakeside Laboratories, Inc.) have suggested its applicability in this regard. Its effectiveness in the prevention of ventricular fibrillation due to benzol and epinephrine in hypothermic and normothermic dogs has been presented in a preliminary report elsewhere. As another phase of this study ventricular arrhythmia was induced by intravenous ouabain in pentobarbital anesthetized dogs. Dactil was administered in a slow, continuous intravenous drip until definite results were determined. Intermittent electrocardiographic tracings were obtained as necessary as a criterion of the status of the rhythm. Amounts of ouabain required to produce a ventricular rhythm varied considerably (0.07 to 0.395 mg./kg.). Dactil was given as a 0.5 to 1.0 per cent saline solution 10 to 50 mg. per minute. Reversion to a supraventricular or normal sinus rhythm occurred in fifteen of twenty experimental procedures completed to date. Present evidence suggests this drug may act in part by depressing ventricular irritability.

SERUM LIPID FRACTIONS IN INDUCED AND SPONTANEOUS HYPOTHYROIDISM; MODIFICATION BY BETA-SITOSTEROL. *M. M. Best,* C. H. Duncan, J. D. Wathen and H. D. Kerman.** Inst. of Medical Research, Univ. of Louisville School of Medicine, Louisville, Ky.

Serum lipid fractions were followed in a group of patients with congestive failure rendered hypothyroid by I-131. Four patients with rheumatic mitral stenosis had initially

low serum total cholesterol values (mean 146, range 109–180). Following I-131 administration they exhibited a transient peak in serum cholesterol during the second month (mean 196, range 181–215). In three of these patients the serum cholesterol followed a similar course, returning four months after treatment to the initial range, while the I-131 uptake remained in the hypothyroid range. For these subjects the mean values were: pre-treatment, 135, second month peak, 189, and return to 147 while the subject was still hypothyroid. In the fourth patient persistent hypothyroidism was associated with an eventual sustained increase in serum cholesterol, from pre-treatment level of 180 to 259 six months later.

Administration of the plant sterol, beta-sitosterol, to this patient and to patients with spontaneous myxedema resulted in a mean reduction of serum cholesterol of 25.9 per cent, comparable to that we have observed from sitosterol administration to euthyroid subjects.

The changes in cholesterol were paralleled by those in serum total lipid and, less consistently, by those in lipid phosphorus and calculated neutral fat.

CLINICAL AND PHYSIOLOGIC EVALUATION OF SEVERAL ORALLY EFFECTIVE BRONCHODILATORS. *H. G. Boren, D. J. George, I. C. Chofnas and C. A. Handley (introduced by C. L. Spurr*)*. V. A. Hospital and Dept. of Medicine of Baylor Univ. College of Medicine, Houston, Tex.

Three orally administered N-substituted arterenol derivatives have been evaluated. Twenty-four male patients, averaging fifty-eight years in age, with continuing difficulty from pulmonary emphysema and chronic bronchitis despite the usual regimen, were studied with special emphasis on pulmonary function. Toxic effects were limited to occasional slight decrease of blood pressure and tachycardia accompanied at times by palpitation or dizziness. No laboratory evidence of hematologic, hepatic, electrocardiographic or renal damage was found, even when drugs were administered over two months. Moderate to marked increase of vital capacity was frequently found. Timed vital capacity, nitrogen washout and flowmeter tracings added no further information.

For study of mechanics, pressure was measured by an intra-esophageal catheter, flow by Lilly flowmeter, volume by electrically recording spirometer. Changes were recorded on multi-channel electrocardiograph and oscilloscope. Mechanics studies on eight patients showed increase frequency of breathing only once, decrease of extremes of pressure fluctuation in seven of eight cases, volume and flow increase in three of four cases, and significant decrease of resistance in three of four patients. Compliance studies in five patients showed an increase twice and decrease once. Of the three drugs studied, N-(2-(3,4-methylenedioxyphenylisopropyl)) norepinephrine hydrochloride (JB251, Lakeside) is most effective. Only mechanical studies allow complete evaluation.

CORRELATION OF PHYSIOLOGIC EFFECTS OF RADIOACTIVE ENDOTOXIN WITH ITS DISTRIBUTION IN VIVO. *A. I. Braude, F. J. Carey, D. W. Sutherland and M. Zalesky (introduced by E. Strauss*)*. Dept. of Internal Medicine, Southwestern Medical School of the Univ. of Texas, Dallas, Tex.

As a means of investigating the pathogenesis of gram-negative bacterial infections, the fate of radioactive endotoxin, labelled with Cr^{51}, was correlated with its physiologic effects after intravenous injection. Endotoxin was prepared by culturing Escherichia coli in the presence only of inorganic constituents to avoid organic impurities which might bind chromium. Firm labelling was achieved by adding $Na_2Cr^{51}O_4$ or $Cr^{51}Cl_3$ directly to endotoxin or living E. coli and radioactivity was directly proportional to toxicity.

Labelled endotoxin, after intravenous injection of lethal doses in rabbits, first appeared in the plasma (but not in the erythrocytes) and then rapidly passed to buffy coat and liver. Tremendous concentrations accumulated in the buffy coat while leukopenia was developing. Rapid removal from plasma was accompanied by fever, leukopenia and sometimes hypotension and diarrhea. Changes in blood volume, determined with Cr^{51} labelled erythrocytes, were variable but not marked.

These results indicate that changes in leukocytes (neutropenia, toxic granulations, reduced mobility) after injection of endotoxin result from localization in them of endotoxin; that localization represents an active removal of endotoxin from the circulation; and that protection against endotoxin, as protection against bacterial infection, depends in part on the ability of leukocytes to ingest endotoxin.

NUCLEOTIDE LEVELS IN HUMAN CARDIAC MUSCLE. *W. J. Burdette.** Chester Beatty Research Inst. of the Royal Cancer Hospital and the Brompton Hospital, London, England.

Fresh, auricular muscle was obtained from eight patients at the time of cardiotomy for mitral stenosis and was placed on ice immediately. After weighing, the myocardium was homogenized and an acid extract prepared. Dowex-1 (200 to 400 mesh) was then used as a formate column to separate the nucleotides. The fractions were collected in volumes of 5 ml., the optical densities of which were read at 260 and 275 mμ in a Beckman model DU spectrophotometer. The results were rather uniform for the various specimens. The average amount (μM/gm.) of AMP was 0.721, of ADP was 0.292, and of ATP was 0.138. Complete separation of other nucleotides was not accomplished but their presence suggests that the adenosine system may not solely be involved in energy exchanges during muscular contraction of the human heart.

CASE OF COLLAGEN DISEASE (SCLERODERMA) IN WHICH PLEUROPNEUMONIA-LIKE ORGANISMS WERE ISOLATED FROM AN OVARIAN CYST. *S. W. Bush, L. B. Robinson, W. E. C. Wacker and T. M. Brown.** Dept. of Medicine, George Washington Univ. School of Medicine, and the Arthritis Research Unit, Medical Service, V. A. Hospital, Washington, D. C.

The case is that of a twenty-nine year old woman with repeated genitourinary infections for five years treated with penicillin. The present illness began five months before hospitalization. Clinical and laboratory studies were compatible with disseminated lupus erythematosus but no L.E. cells were found. Recurrent Escherichia coli urinary infections were treated with antibiotics other than penicillin. Cortisone was employed intermittently for symptomatic control. Laparotomy disclosed a follicular ovarian cyst. The clear cystic fluid contained pleuropneumonia-like organisms in pure culture. Improvement after surgery was followed by a downhill course. Treatment consisted of cardiac management and cortisone therapy. Autopsy, after fifteen months of illness, revealed findings compatible with scleroderma in the skin, gastrointestinal tract, lungs and heart.

This is the first case in which pleuropneumonia-like organisms (L organisms) were obtained from an ovarian cyst. These findings are interesting in view of the long-standing speculation regarding the role of pleuropneumonia-like organisms in Reiter's disease, genitourinary infections, rheumatoid arthritis and rheumatic fever. Also, the findings may pertain to the known ability of penicillin to induce the formation of 'L' forms from common bacteria. No conclusions regarding the etiology of collagen diseases can be drawn from an isolated case but additional studies appear indicated.

THE LEUKOPENIA OF VIRUS INFECTION—RELATION TO THE CONCENTRATION OF VIRUS AND THE VIRAL LESION. *G. R. Cary, W. B. Sorrell and E. D. Kilbourne.** Dept. of Medicine, Tulane Univ. School of Medicine, New Orleans, La.

The well known leukopenia of virus infections is an enigmatic phenomenon which has received little study. With the belief that investigations on the genesis of this leukopenia might aid in elucidation of the pathogenesis of viral disease, a study was undertaken of experimental influenza virus infection. Adult male CFW mice weighing 20–22 gm. were inoculated intranasally with either 10^6 EID_{50} of influenza A virus (PR8 strain) or a control injection of saline. Both inocula contained penicillin and streptomycin. At varying intervals following infection (twelve, twenty-four, forty-eight, seventy-two and ninety-six hours) mice (four/group) were bled from the tail, then killed for study of pulmonary lesions, pulmonary virus concentrations and bone marrow cytology.

A 22 per cent decrease in the total leukocyte counts of virus-infected mice was noted forty-seven to ninety-six hours after inoculation. Differential counts revealed an absolute lymphopenia representing a 40–45 per cent reduction in lymphocytes and a concomitant, absolute neutrophilia. Leukopenia occurred twenty-four hours *subsequent* to the logarithmic phase of viral increase, *coincident* with the attainment of maximal viral concentration, and twenty-four hours *prior* to the appearance of pneumonia. Thus infection of a murine host with influenza virus results in an absolute lymphopenia and an absolute neutrophilia temporally related to the peak of virus increase but prior to the appearance of the gross viral lesion.

VASOACTIVITY OF AZIDES IN HYPERTENSION. *P. Comens (introduced by H. A. Schroeder**).* Hypertension Div., Dept. of Internal Medicine, Washington Univ. School of Medicine, St. Louis, Mo.

Utilizing photoelectric plethysmographs, photographic recordings were made in dogs after

intraarterial injections of choline azide (0.4 mg./kg.) and sodium azide (0.1 mg./kg.). Both produced unilateral local vasodilatation in the extremities of ten normotensive dogs, more marked with choline azide. A mean drop in diastolic pressure of 33 mm. Hg at fifteen minutes for both was more prolonged with the choline salt. Toxic doses of the latter (4.0 mg./kg.) caused marked electrocardiographic abnormalities. Two unanesthetized renal hypertensive dogs with blood pressures of 250/150 and 300/160 mm. received ten daily oral doses of choline azide; mean diastolic pressures dropped 44 to 64 mm. Hg for as long as five hours with recovery in twenty-four hours. When given intravenously, both drugs caused negligible late depressor effects in anesthetized normotensive rats. However, some operated animals showed significant diastolic depression only with choline azide. This agent administered gastrically caused insignificant changes in normotensive but marked prolonged depression in hypertensive rats. Neither agent blocked the pressor action of nor-epinephrine *in vivo*, although by the rabbit aorta strip method of Furchgott 0.05 mg. choline azide blocked the action of 2.0 γ nor-epinephrine. Sodium azide (5.0 mg.) used for long periods in four hypertensive patients at four-hourly intervals caused little or no effect upon blood pressure. These results suggest that choline azide is a long acting vasodilator when given orally to rats and dogs.

EFFECT OF L-TRIIODOTHYRONINE ON PROTEIN SYNTHESIS RATE MEASURED WITH N^{15} GLYCINE IN PATIENTS WITH PRIMARY MYXEDEMA. *K. R. Crispell,* W. Parson* and G. F. Hollifield.* Dept. of Internal Medicine, Univ. of Virginia School of Medicine, Charlottesville, Va.

The amino acid pool and the protein synthesis rate has been determined in five patients with primary myxedema using isotopic nitrogen, N^{15}. The patients were studied under the usual metabolic regimen. An interesting but unexplained finding was a moderate degree of positive nitrogen balance as determined by classic nitrogen studies. However, the protein synthesis rate as determined by the isotopic technic was consistently decreased in patients with myxedema. The average in the five patients was 379 mg./kg. per twenty-four hours (range 180–490) as compared with an average of 756 mg./kg. per twenty-four hours in five healthy volunteers (range 610–970). The size of the amino acid pool was not consistently altered.

Studies will be presented which show that several days after first administering L-triiodothyronine there is no increase in the protein synthesis rate. However, after administering the L-triiodothyronine for six to nine months the protein synthesis rate was markedly increased. For example, in one patient there was an increase in protein synthesis rate from 350 mg./kg. per twenty-four hours to a high of 1,300 mg./kg. per twenty-four hours.

HYPERACTIVITY OF THE BLOOD COAGULABILITY CONTROL MECHANISM—A POSSIBLE CAUSE OF IRREVERSIBLE SHOCK. *J. W. Crowell and W. L. Read (introduced by A. C. Guyton*).* Dept. of Physiology and Biophysics, School of Medicine, Univ. of Mississippi, University, Miss.

If an animal is bled until his arterial pressure is very low and this pressure level is maintained for a long period of time, a slowly falling blood pressure develops which continues to fall although the withdrawn blood is reinjected. Transfusion of additional blood or injection of sympathomimetic drugs has only a temporary effect, for the animal eventually dies. This is a type of irreversible shock.

Experiments in our laboratory have shown that concurrent with the fall in arterial pressure there is also a fall in the coagulation time of the circulating blood and that this hypercoagulability predisposes to the formation of large numbers of very small blood clots. If hypotension continues long enough for a major portion of the lung capillaries to be blocked, then the pulmonary resistance becomes so great that adequate circulation cannot be maintained. By use of large doses of heparin given before the beginning of the period of hypotension, the mortality rate from the hemorrhagic shock experiment is greatly lessened. Only one of ten dogs given heparin developed irreversible shock as compared with nine of ten dogs given no heparin.

CLINICAL RESULTS WITH PENTOLINIUM IN TREATMENT OF HYPERTENSION; COMPARISON WITH HEXAMETHONIUM WHEN BOTH ARE USED IN COMBINATION WITH RAUWOLFIA. *E. Dennis, R. Ford, W. Hughes, R. Hershberger and J. H. Moyer.** Baylor Univ. College of Medicine, Houston, Tex.

Recent reports by Freis and his co-workers have indicated that pentolinium is superior to other anti-hypertensive agents. In order to

evaluate the relative effectiveness of this agent, two groups of hypertensive patients were studied. Following adequate control observations, fifteen patients in Group I were given a combination of Rauwolfia and pentolinium. Group II was composed of sixty patients who received a combination of Rauwolfia and hexamethonium as therapy for six months to a year; these patients were then given a combination of Rauwolfia and pentolinium and the response rate, side reactions and tolerability of the drugs were compared. The results indicate that the small group of fifteen patients started on pentolinium and Rauwolfia (Group I) showed a 100 per cent response; 75 per cent of the patients in Group II responded to Rauwolfia in combination with hexamethonium; 73 per cent (forty-four patients) responded to Rauwolfia plus pentolinium; 10 per cent responded to neither combination; 15 per cent responded to Rauwolfia and pentolinium who had not previously responded to Rauwolfia and hexamethonium. On the other hand, 17 per cent who were previously responsive to Rauwolfia and hexamethonium were not responsive to Rauwolfia plus pentolinium. It is concluded that hexamethonium and pentolinium have a comparable effect in reducing the blood pressure when used in combination with Rauwolfia. The incidence and severity of side effects appears to be qualitatively similar but possibly less prolonged with pentolinium.

CORRELATION OF VENTRICULAR ELECTROKYMOGRAMS AND KINETOCARDIOGRAPHIC TRACES; APPLICATION TO STUDY OF MOVEMENTS OF THE HUMAN HEART. *E. E. Eddleman, Jr.* (*introduced by T. R. Harrison**). Dept. of Medicine, Medical College of Alabama, and Medical Service, V. A. Hospital, Birmingham, Ala.

Precordial chest wall movements (kinetocardiograms) were studied in a number of normal subjects as well as electrokymographic traces taken from many points of the ventricular borders. In addition simultaneous kinetocardiograms and electrokymograms were obtained in a few subjects. The similarities between the electrokymographic traces and the kinetocardiograms suggest that the movements of the precordium are primarily related to the movements and shape changes of the heart. By correlating the precordial movements with the electrokymographic traces from many points over the ventricular borders, a hypothesis for the movements of the normal heart can be arrived at: (1) anterior swing of the heart .02 second after the onset of the QRS complex, probably as the result of right ventricular contraction, (2) shortening of the heart and right ventricular inflow contraction, (3) apex thrust, possibly as the result of a physiologic aneurysm, (4) sphincteric squeeze of the entire ventricular walls, (5) elongation of the heart and inflow tract relaxation, (6) right ventricular relaxation with leftward and posterior swing of the heart, (7) filling and anterior rebound of the heart as the left ventricle relaxes.

BLOOD VOLUME IN PATIENTS WITH LAENNEC'S CIRRHOSIS AS DETERMINED BY RADIOACTIVE CHROMIUM TAGGED RED CELLS. *S. Eisenberg* (*introduced by A. Goth**). Dept. of Internal Medicine, Southwestern Medical School of the Univ. of Texas, and the Medical Service and Radioisotopes Unit of the V. A. Hospital, Dallas, Tex.

Twenty subjects with Laennec's cirrhosis were studied by the radiochromium tagged red cell technic. Nineteen patients had ascites; none had bled for a four-month period prior to the study. Comparisons were made between pre- and post-treatment values and between these and the values in a group of twenty normal persons.

Results: (1) Plasma volume was increased 41 per cent and blood volume 29 per cent in patients with esophageal varices and/or cyanosis; in the absence of these features these measurements were normal. (2) Despite lowered hemoglobin values, the red cell mass was normal in the twenty subjects studied suggesting that the "anemia of liver disease" may frequently be due to hemodilution. (3) In four cyanotic subjects the red cell mass was 49 per cent greater than normal. (4) Inconsistent changes in plasma volume followed clinical improvement and recession of ascites.

These findings suggest in the absence of evidences of an expanded vascular bed or a stimulus to erythropoiesis, the blood volume in Laennec's cirrhosis is normal; and "anemia of liver disease" is often a result of hemodilution.

EFFECT OF CEREBRAL CORTICAL STIMULATION IN CATS UPON EPINEPHRINE ACTIVITY AS INDICATED BY BLOOD LACTIC ACID LEVELS. *R. W. Ferguson, M. G. Mitts, M. Bernhaut and E. C. Hoff* (*introduced by J. L. Patterson, Jr.**). Dept. of Medicine and Neurologic Science, Medical College of Virginia, Richmond, Va.

The present studies were undertaken to determine whether stimulation of cerebral cortical areas, known to mediate autonomic responses, would also evoke increased adrenal medullary activity. The blood lactic acid concentration was used as the indicator of increased epinephrine secretion, since DiSalvo and colleagues (1953) demonstrated its validity for this purpose, in the absence of muscular movement or hypoxia. Acute experiments were performed under ether anesthesia, using d-tubocurarine and intermittent positive pressure breathing. Inductorium or rectangular-wave stimuli lasting ten seconds were delivered at intervals to loci on left and right anterior gyri alternately over a period of one hour with resulting transient hypertension, pupillary dilatation and nictitating membrane retraction. Blood lactic acid determinations made on fifteen stimulated cats and eleven unstimulated control animals (subjected to identical surgical procedures) showed a mean rise of 27 mg./100 ml. in the stimulated and 12.5 mg./100 ml. in the controls, a difference statistically significant ($p < .01$). Cats prepared surgically the day prior to the experiment in order to diminish stress showed lower initial lactate concentrations and greater increases with stimulation.

It is concluded that electrical stimulation of anterior sigmoid loci of the cerebral cortex causes increased secretion of epinephrine from the adrenal medulla.

CEREBRAL BLOOD FLOW, CARDIAC OUTPUT, CARDIAC WORK, MEAN ARTERIAL PRESSURE AND RIGHT HEART PRESSURE DURING POSTURAL SYNCOPE. *F. A. Finnerty, Jr., E. A. Partenope, J. F. Fazekas,* J. C. Rose and L. S. Lilienfield.* Dept. of Medicine, Georgetown Univ. School of Medicine and the Georgetown Univ. Medical Division, District of Columbia General Hospital, Washington, D. C.

In an attempt to clarify the pathogenesis of postural syncope cerebral and cardiac hemodynamic studies were performed in the 40° head-up tilt. Cerebral hypoxia was induced by lowering the arterial pressure acutely with intravenous hexamethonium and/or by posture. In the heterogeneous group of forty-six subjects studied, although the level of arterial pressure at time of syncope varied between 100.7 and 40.9 mm. Hg, signs of cerebral hypoxia developed when the cerebral blood flow was reduced to 31.5 cc./min./100 gm. brain (standard error 0.98). With the onset of cerebral hypoxia, right ventricular pressures decreased sharply, intracardiac pressure waves broadened and flattened, and direct Fick cardiac outputs measured in twelve subjects showed an average reduction of 42.6 per cent with a range of 20 to 68 per cent. Cardiac work was reduced by more than 70 per cent in all patients, which together with the production of bradycardia explained the absence of angina and electrocardiographic changes.

These observations are consistent with the concept that the mechanism of cerebral hypoxia was due to loss of vasoconstrictor tone which in these tilted subjects prompted failure of venous return, decrease in right ventricular pressure, decrease in cardiac output and finally, a decrease in cerebral blood flow below the critical level.

METABOLIC EFFECT OF QUINIDINE; EVIDENCE SUGGESTING IMPAIRMENT OF GLUCOSE UTILIZATION. *R. H. Furman* and R. P. Howard.** Cardiovascular and Endocrinology and Metabolism Sections of the Oklahoma Medical Research Foundation, and the Dept. of Medicine, Univ. of Oklahoma School of Medicine, Oklahoma City, Okla.

Since our initial report of nitrogen retention ("protein anabolic effect") during the administration of quinidine sulfate to human subjects, seven additional subjects have been studied. Complete metabolic balance studies were carried out in five, and significant nitrogen retention without salt or water retention was noted in four subjects.

Studies of carbohydrate metabolism were carried out in three subjects: a forty-two year old man with remote myocardial infarction and two half-brothers, aged ten and six, with Von Gierke's disease (hepatic only). Glucose tolerance curves during quinidine administration revealed significantly impaired tolerance when compared with control curves. Because of the possibility that quinidine may alter cell permeability to insulin, further tolerance studies are underway in additional subjects utilizing both glucose and fructose. According to Uyeki, Geiling and Dubois quinidine sulfate inhibits the oxidation of glucose, pyruvate and certain other substrates by rat heart slices, possibly by inhibiting transphosphorylating enzymes.

EXPERIMENTAL BLOOD COOLING TO 1.5°C. WITH A PUMP-OXYGENATOR FOR OPEN CARDIAC SURGERY. *F. Gollan (introduced by G. R. Meneely*).*

Research Laboratory and Radioisotope Unit, Thayer V. A. Hospital, Nashville, Tenn.

Cardiac surgery during hypothermia alone is limited by the short period of inflow occlusion and ventricular fibrillation; extracorporeal circulation has its drawback by the complexity of apparatus, the large coronary flow and the danger of air embolism. By a combination of the two approaches these difficulties were overcome. The entire venous return to the right heart was shunted into a pump-oxygenator, refrigerated and returned under pressure into the aorta. When satisfactory artificial oxygenation was achieved the respirator was turned off. At 13°C. the heart stopped beating and the left atrium or ventricle was opened. The heart chambers were empty and, due to cardiac arrest, coronary air embolism did not occur. After about thirty minutes of cardiac arrest the heart was closed, the blood was rapidly rewarmed in the extracorporeal circulation and normal cardiac and respiratory functions returned. The lowest body temperature reached was 1.5°C. Thirteen dogs survived this procedure without evidence of cerebral or cardiac damage. Four animals died of postoperative complications. Nine dogs were observed for one month.

RELATIONSHIP OF RIGHT ATRIAL PRESSURE TO CARDIAC OUTPUT FOLLOWING MYOCARDIAL DAMAGE. *A. C. Guyton,* A. W. Lindsey and B. N. Kaufmann.* Dept. of Physiology and Biophysics, Univ. of Mississippi School of Medicine, University, Miss.

In quantitative experiments on dogs, the following dual effects of right atrial pressure on cardiac output have been studied: Increasing the right atrial pressure increases the filling pressure in the heart itself and therefore increases the cardiac output; this is the well known Starling's law. Increasing the right atrial pressure also causes increased back pressure in the veins, which decreases the return of blood from the peripheral vessels to the heart. When these two opposing effects are equated, right atrial pressure automatically assumes a level which allows the venous return to the heart to equal the output from the heart. The quantity of blood pumped by the heart is determined not only by the filling pressure in the right ventricle but also by the integrity of the cardiac muscle itself, for a progressively damaged myocardium pumps progressively less blood at any given right atrial pressure. Increasing the blood volume increases the right atrial pressure and partially overcomes the diminished cardiac output due to myocardial damage. Graphs have been constructed to depict how varying degrees of myocardial damage and varying fluid volumes determine right atrial pressure and cardiac output simultaneously.

MALIGNANT HYPERTENSION: INFLUENCE OF RETINOPATHY, UREMIA AND UNDERLYING RENAL DISEASE ON MORTALITY AND SURVIVAL TIME. *J. A. Hagans, A. A. Brust* and E. B. Ferris.** Dept. of Internal Medicine, Emory Univ. School of Medicine and Grady Memorial Hospital, Atlanta, Ga.

Sixty-four patients with untreated malignant hypertension have been studied over an average observation period of four years. Duration of study was sufficient to evaluate the natural course since 88 per cent of the patients were dead at the close of the study.

The presence or absence of uremia was the only important factor in mortality. Grade 3 fundi, grade 4 fundi, underlying chronic renal disease or "essential" hypertension did not influence mortality figures. Mortality for the period of study was strikingly less in those without uremia at initial contact (70 per cent); all patients with uremia were dead. Mortality was similar in patients with grade 3 and grade 4 fundi (87 per cent and 88 per cent, respectively) but the grade 3 patients survived much longer (18.8 months) than the grade 4 (3.3 months). This difference was in patients without uremia as there was no difference in survival time of patients with grade 3 and 4 fundi who had uremia initially (all this holds true in both chronic renal and essential hypertensive groups). Uremic patients with chronic renal disease lived longer (6.4 months) than uremic patients in the essential hypertensive group (1.3 months).

HEMATOLOGIC STUDIES IN HEAT STROKE: THE ANEMIA OF HEAT STROKE WITH EMPHASIS ON A HEMOLYTIC COMPONENT. *E. R. Halden, F. Jones, D. A. Sutherland and E. E. Muirhead.** Depts. of Medicine and Pathology, The Univ. of Texas Southwestern Medical School, Dallas, Tex.

Fifteen patients with heat stroke were studied. The rectal temperature varied between 106–112°F. (10 between 108–112°F.). There were two age groups: seven aged thirty-two to fifty-four years (average, forty-six), eight aged sixty-three to ninety-seven years (average, seventy-five). The initial peripheral hemoglobin of 11.6–16 gm./

100 cc. (average 13.6) decreased within about one week to 8.2–13.8 gm. (average, 10.7). There was no obvious blood loss. By autotransfusion the survival of the patient's RBC was studied by the radiochromium method in thirteen patients. An increased rate of RBC destruction was detected in ten patients. The mean life-span values were: thirty to forty-five days for six, fifty to eighty days for four. Four-day stool urobilinogen in six patients averaged 242 mg. per day, giving a hemolytic index of about two times the upper limits of normal. Additional findings included: normal or slightly elevated WBC; slight reticulocytosis in five patients; thrombocytopenia in all (platelets < 100,000 in eleven); elevated ESR; elevated initial eosinophil count (680–1,300 per cu. mm.); prolonged clotting time in five patients; evidence of cell injury in the peripheral blood and bone marrow.

The anemia of heat stroke is partly due to a hemolytic state and partly due to injury to the bone marrow. It is plausible to consider the hemolysis related to the capillary stasis of this condition.

EFFECT OF RESERPINE ON THE HYPOTHALMIC PRESSOR RESPONSE. *F. Harrison and A. Goth.** Dept. of Anatomy, Pathology and Pharmacology, The Univ. of Texas Southwestern Medical School, Dallas, Tex.

The postulated hypothalamic site of action of reserpine was tested by direct electrical stimulation using the stereotaxic technic. Under chloralose urethane anesthesia, blood pressure was recorded in twelve cats. The hypothalamus was stimulated repeatedly before and after the injection of reserpine (100–200 μg./kg.). In addition, epinephrine or L-norepinephrine was injected repeatedly in order to estimate vascular responsiveness to the sympathetic mediators. The following effects were observed following reserpine: progressive increase in responsiveness to injected epinephrine, gradual hypotension, bradycardia, moderate to marked decrease in the height and alteration of the shape of the pressor response to hypothalamic stimulation. The hypothalamic pressor response, following the initial depression, returned in some experiments to normal or even above. In these cases, however, there was such an exaggeration of the pressor effect of injected adrenergic drugs that this phenomenon may be due to increased vascular responsiveness rather than the return to normal sensitivity of neural structures. In acute spinal animals in which there is already hypotension and increased responsiveness to epinephrine, reserpine causes no further such effects. These results support the hypothesis that reserpine depresses the hypothalamus or its descending sympathetic pathways.

SYSTOLIC MOVEMENTS OF THE PRECORDIUM AND OF THE BODY IN PATIENTS WITH BUNDLE BRANCH BLOCK. *T. R. Harrison,** *E. E. Eddleman and T. J. Reeves.* Dept. of Medicine, Medical College of Alabama, and the Medical Service of the V. A. Hospital, Birmingham, Ala.

In normal subjects there is a sharp inward movement of the parasternal region about .03 second before the onset of the carotid upstroke. This is thought to represent right ventricular ejection. In patients with right bundle branch block the time from the beginning of the QRS to the onset of the carotid upstroke is slightly prolonged while the time from the onset of the QRS to the sharp parasternal inward movement is more markedly prolonged. In patients with left bundle branch block the time from the ECG onset to right ventricular ejection appears to be slightly prolonged while the time elapsing between the onset of the QRS and the beginning of the carotid upstroke is markedly prolonged. It would appear that the contraction of each ventricle contributes somewhat to expulsion by the other ventricle. The onset of the G-H upstroke and of the H-I downstroke of the ballistocardiogram is markedly delayed in right bundle branch block but there is minimal or no delay in patients with left bundle branch block. This suggests that structures activated by the right bundle play a predominant role in the genesis of these headward-footward movements of the body. The precordial movements likewise tend to show alterations in the two conditions.

RENAL HEMODYNAMIC RESPONSE TO PENTAPYRROLIDINIUM; COMPARISON WITH HEXAMETHONIUM. *R. L. Hershberger* (*introduced by J. H. Moyer**). Baylor Univ. College of Medicine, Houston, Tex.

Pentapyrrolidinium is a ganglionic blocking agent of the quaternary ammonium group structurally related to hexamethonium but believed to have fewer side effects. Since this agent has been reported to be superior to hexamethonium in the treatment of hypertension, a series of patients was studied for the effects of pentapyrrolidinium on renal hemodynamics in hypertension. Nine patients re-

ceived continuous intravenous infusions and eight received single intravenous doses during renal clearance studies. These were compared with previous studies using hexamethonium. It was shown that: (1) Pentapyrrolidinium produced a more pronounced and prolonged hypotension than that produced by hexamethonium. (2) After initial reduction in mean blood pressure by both continuous infusion and single injection of pentapyrrolidinium, glomerular filtration rate and renal blood flow were significantly depressed. Three hours after a single injection these functions increased significantly and approached control levels despite maintained hypotension. With continuous infusions, however, both GFR and RBF remained depressed. (3) Sodium and water excretion were depressed initially and remained depressed. (4) Potassium excretion was not significantly altered. The over-all effect of pentapyrrolidinium on renal hemodynamics was essentially the same as that found with intravenous hexamethonium. Differences found were a reflection of the greater reduction of pressure produced by pentapyrrolidinium.

ACUTE ELEVATION OF HEPATIC VENOUS AND ARTERIAL SERUM POTASSIUM DURING HYPERVENTILATION. *J. B. Hickam,* W. P. Wilson and R. Frayser.* Depts. of Medicine and Psychiatry, Duke Univ. School of Medicine, Durham, N. C.

In the first one to two minutes of voluntary hyperventilation there appears a shift of the arterial CO_2 dissociation curve in a direction which considerably accentuates the alkalinity of the serum. This proves to result from an acute rise in serum potassium, averaging 1.3 mEq./L. after two minutes of hyperventilation (twelve subjects). In looking for the source of this potassium it was found that jugular venous and peripheral venous potassium concentrations are slightly below arterial, but that hepatic venous serum has a much higher potassium content during hyperventilation than blood from any other site. In four subjects the mean increase in hepatic venous potassium was 2.3 mEq./L. The mechanism of this outpouring of potassium from the splanchnic region during early hyperventilation is not yet established.

This phenomenon accounts for about 25 per cent of the pH rise during early hyperventilation. It may well play a significant part in certain of the phenomena associated with hyperventilation, such as tetany, electrocardiographic changes, and possibly some of the acute vasomotor responses. The mechanism of this potassium rise may be related to that reported to occur when severe respiratory acidosis is abruptly relieved by overventilation, as in anesthesia during thoracic surgery.

METABOLIC AND PSYCHOLOGIC STUDIES ASSOCIATED WITH COLLEGE ROWING. *S. Richardson Hill, Jr., H. M. Fox, B. Murawski, S. J. Gray, J. R. St. Marc and G. W. Thorn (introduced by T. R. Harrison*).* Dept. of Medicine, Peter Bent Brigham Hospital, and Harvard Medical School, Boston, Mass.

This study was designed in an attempt to clarify further the role of the adrenal cortex and various psychologic factors in the human response to stress. The subjects were members of a 1954 college varsity crew studied for six days during the final two weeks of preparation for the four-mile Harvard-Yale race. Eosinophil counts were taken at 9 A.M., 5 P.M. and 9 P.M. Four-hour urine specimens were collected from 9 A.M. to 9 P.M. and one specimen from 9 P.M. to 9 A.M. for determination of the 17-hydroxycorticoid, 17-ketosteroid and uropepsin excretion. Psychologic measurements included two Rorschach tests, individual Thematic Apperception Tests and personal interviews.

The eosinophil response showed a mean 20 per cent increase on the control day, a 30 per cent decrease on the regular practice day, a 69 per cent decrease on the time trial day and a 70 per cent decrease on the race day, over the same 5 to 9 P.M. period. The 17-hydroxycorticoid and 17-ketosteroid data revealed highly significant ($P < .01$) differences between individuals and between the race day as compared to the control and practice days, with no significant difference between values on the control day as compared with the practice day. On race day there was an obliteration ($P < .01$) of the daily diurnal decrease in 17-hydroxycorticoids. Certain correlations have been made between metabolic response and personality structure.

STUDY OF THE QUANTITATIVE RELATIONSHIP BETWEEN ANTIDIURETIC HORMONE AND RENAL TUBULAR REABSORPTION OF WATER. *W. Hollander, Jr., T. F. Williams, C. C. Fordham, III, and L. G. Welt.** Dept. of Medicine, School of Medicine, Univ. of North Carolina, Chapel Hill, N. C.

The rate of excretion of urine and the clearance of free water during physiologic diabetes

insipidus have been compared with those values observed during various constant rates of infusion of pitressin,® in healthy young adult males. A positive balance of water of approximately 1 L. was maintained throughout each study.

At relatively constant rates of solute excretion, the changes in the rates of excretion of urine (ΔV) and clearance of free water (ΔC_{H_2O}) are approximately equal and represent the increased rate of renal reabsorption of water resulting from the administered pitressin. At rates of infusion of pitressin between one and twenty milli-units per hour, the increase in rate of renal tubular reabsorption of water appears to vary as an exponential function of the rate of administration of pitressin according to the equation: $\Delta C_{H_2O} = 2.7$ (pitressin rate)$^{0.52}$. Although not yet established unequivocally, the generality of this or a similar relationship is suggested by the high degree of statistical significance with which the data fit this equation.

It is inferred that, in the range studied, the increase in renal tubular reabsorption of water promoted by pitressin is approximately a function of the square root of the rate of administration of pitressin.

ABSORPTION, TRANSPORT AND EXCRETION OF Cu^{64} IN THE NORMAL HUMAN AND IN PATIENTS WITH WILSON'S DISEASE. *W. N. Jensen and H. Kamin (introduced by T. B. Schwartz.*)* Depts. of Medicine and Biochemistry, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

Non-isotopic copper studies have shown that there is a constant increase in brain and liver copper content, hypocupremia and hypercupuria in Wilson's disease.

Cu^{64} was administered orally to four normal subjects and three patients with Wilson's disease. Radiocopper content of blood, plasma, urine and feces was measured over a sixty-hour period. All normals had an initial peak of plasma non-globulin-bound radiocopper, a decline during the next six to eight hours; followed by a second, progressive increase present during the remainder of the study. The secondary rise consists of globulin-bound radiocopper. In Wilson's disease there was no secondary rise in total plasma or globulin-bound radiocopper. Urinary excretion correlated with the increased plasma non-globulin radiocopper. Fecal excretion of radiocopper was decreased.

It is suggested that copper is transported from the intestine to the liver; incorporated into a copper-globulin complex and released to the plasma. The initial peak of non-globulin-radiocopper represents leakage around the copper-globulin binding mechanisms when these are presented with increased quantities of copper. One defect in Wilson's disease consists of a metabolic block at the copper globulin synthesis and/or release stage. Other abnormalities in copper metabolism may be secondary to this defect.

ANALYSIS OF THE CHEMICAL EVENTS AND THEIR INTERRELATIONSHIPS WITH ALTERATIONS IN ECG DURING RESPIRATORY ACIDOSIS AND ALKALOSIS. *S. B. Joyner, D. A. Davis, D. T. Young, E. Craige and L. G. Welt.** Univ. of North Carolina School of Medicine, Chapel Hill, N. C.

The chemical alterations induced by respiring high concentrations of CO_2, and hyperventilation with room air, have been studied in three groups of dogs as follows: (1) simultaneous arterial and central venous blood, (2) simultaneous arterial, peripheral and hepatic venous blood, and (3) arterial blood samples in experiments conducted forty-eight hours following nephrectomy and injection with inulin. The effects of hypercapnia are: decrease in pH, increase in pCO_2, increase in inulin space, and an accession of sodium, potassium, glucose and phosphorus to the inulin space. The increment of sodium and potassium appears to be derived from the muscles, glucose from the liver (splanchnic area), and phosphorus from both. Hyperventilation promotes: an increase in pH, and a decrease in pCO_2, an increase in the inulin space is again observed, and larger increments of sodium and potassium, with smaller accessions of glucose, and inconstant increments of phosphorus to the inulin space. Sodium appears to leave muscle and liver, potassium is lost from liver but gained by muscle. The liver releases glucose, and both liver and muscle release phosphorus.

The alterations in the ECG are not consistently predictable in terms of pH, pCO_2 or the concentrations of potassium in serum.

RENAL SODIUM REGULATION: A COMPARISON OF THE EFFECT OF RECUMBENCY AND NECK COMPRESSION. *G. A. Kelser, Jr., H. L. Izlar, E. H. Estes, Jr. and J. V. Warren.** Dept. of Medicine, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

Sodium excretion has been reported to increase upon changing from the sitting to the recumbent position and upon compressing the neck of normal sitting subjects. Observations have been made on eight healthy individuals to estimate the magnitude of the effect of these maneuvers. Hourly urinary sodium values were obtained on a control day with the subjects in a sitting position drinking 200 ml. of a 0.14 per cent sodium chloride loading solution every thirty minutes. The fifth through the eighth hours were designated test periods. In the test period on subsequent days either the horizontal position was assumed or a cuff was inflated around the neck to a pressure of 20 mm. Hg in the sitting position.

Recumbency produced a significant increase in sodium excretion in the seventh, eighth and ninth hours when compared with the control day ($p < 0.01$) and with the control period on the test day ($p < 0.01$). However, the values on the neck compression day were not significantly different from the control day ($p > 0.5$) or the control period on the test day ($p > 0.5$). It is concluded that this experimental design affords a valid method of investigation not only of the presence of sodium regulatory mechanisms but of their comparative importance.

Effects of ACTH and Rothane on the Renal Clearance of Thiosulfate. *W. M. Kelsey, E. H. Yount, and J. M. Little.** Depts. of Pediatrics, Medicine and Pharmacology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

During the course of a study of the effect of ACTH and rothane on renal function in the dog 137 simultaneous measurements of C thiosulfate and C inulin were made under four circumstances: (1) control, (2) ACTH, (3) rothane and (4) rothane plus ACTH. ACTH increased the C thiosulfate and statistically altered the C thiosulfate C inulin ratio when compared to control values. Rothane lowered the C thiosulfate and also resulted in an altered C thiosulfate/C inulin. Rothane plus ACTH raised the C thiosulfate above control values but not to the level when ACTH was given alone. Pregnant dogs responded differently than nonpregnant animals when ACTH was given.

It is suggestive that in the dog the renal clearance of thiosulfate approximates the GFR but does not actually measure it since it is significantly less than the C inulin. During ACTH administration the C thiosulfate equals the C inulin. This suggests that ACTH decreases the renal tubular absorption of thiosulfate. Increase in the excretion of thiosulfate was not accompanied by detectable changes in electrolyte or water re-absorption.

Effects of Angiotonin on Pulmonary Artery Pressures of Acute Goldblatt Dogs. *W. L. Kenoyer, L. G. May, A. Bennett, S. Y. Tsai and R. Gregory.** John Sealy Memorial Laboratory and Dept. of Internal Medicine, Univ. of Texas Medical Branch, Galveston, Tex.

Pulmonary artery pressures are normal in hypertensive patients. We have observed that this is true in dogs made chronically hypertensive by the Goldblatt method. It was further noted that angiotonin was capable of elevating pulmonary artery pressures as well as systemic pressures in normotensive and hypertensive patients and dogs.

Since long-standing renal hypertensive dogs may have normal pulmonary artery pressures due to some adaptive mechanism, it was thought necessary to make similar studies in dogs made acutely hypertensive. Seven dogs were made hypertensive by the Goldblatt technic. Pulmonary artery and systemic pressures were measured in these animals before and at intervals following the development of systemic hypertension. In no case was the pulmonary arterial pressure elevated. In six dogs angiotonin was given during the acute phase of systemic hypertension. Each dog responded to angiotonin with an elevation of pulmonary and a further elevation of systemic pressures.

These data do not support the concept that acute renal hypertension in dogs is due to angiotonin.

Concentration of Tetracycline in the Serum Following Parenteral Administration. *B. Kent, E. Shoemaker, E. Townsend, B. Bennett and E. M. Yow.** Baylor Univ. College of Medicine, and the Jefferson Davis and V. A. Hospitals, Houston, Tex.

This study was designed to evaluate the level of tetracycline attained in the serum, the time of peak levels and the duration of significant levels following parenteral administration of the antibiotic. Fifty patients were given either single intramuscular injections, single intravenous injections or intramuscular injections at eight-hour intervals over a five-day period. The doses

ranged between 50 mg. and 500 mg. of the antibiotic. An additional group of patients with either hepatic or renal impairment were given the antibiotic and were compared with the normal patients. Serum was collected at intervals over a twenty-four-hour period following single injections and daily in those patients receiving multiple injections. The concentration of the drug in the serum was determined by the twofold serial dilution method.

Following single intramuscular injections peak levels were reached in four hours, significant levels being sustained for eight hours following 100 mg. injections and twelve hours following larger doses. These levels were approximately twice as high as levels previously reported for equivalent oral doses. A tendency toward accumulation was noted only within 250 mg. multiple doses. High levels were attained by intravenous administration of the drug, however, these were of shorter duration than those following intramuscular injection.

RENAL RESPONSE TO AMMONIUM CHLORIDE ACIDOSIS IN GLYCOSURIC OSTEOMALACIA. *L. H. Kyle,* J. J. Canary and R. J. Meyer.* Dept. Medicine, Georgetown Univ. School of Medicine, Washington, D. C.

Renal tubular disorders associated with osteomalacia comprise two major groups. One is characterized by hyperchloremic acidosis, and the skeletal demineralization is attributed to cation loss secondary to impaired urinary acidification. The other group, known as the Fanconi syndrome, manifests glycosuria and other reabsorptive defects. Although acidosis may occur in this type of tubular insufficiency, its mechanism has received inadequate study.

Blood and urinary changes were followed during induction of ammonium chloride acidosis in three patients with glycosuric osteomalacia. The first patient, who had the infantile form of the disorder with cystinosis, showed a normal serum chloride, low bicarbonate and loss of bicarbonate in the urine. Acid loading caused no increase in ammonia production. The second patient demonstrated numerous reabsorptive defects and the chemical pattern of hyperchloremic acidosis. Minimal augmentation of urinary ammonia and titratable acidity resulted from administration of chloride. The third patient had glycosuria and hyperphosphaturia but the serum chloride and bicarbonate concentrations were normal. In this case, renal base-sparing mechanisms responded normally to administration of ammonium chloride.

These studies indicate that the two renal syndromes are not clearly separable and suggest the presence of factors other than cation loss in causation of osteomalacia.

EFFECT OF BLOOD TRANSFUSIONS IN PATIENTS WITH PERNICIOUS ANEMIA. *B. S. Leavell* and J. D. Mason, Jr.* Dept. of Internal Medicine, School of Medicine, Univ. of Virginia, Charlottesville, Va.

In 1946 Davidson et al. reported that in pernicious anemia in relapse multiple transfusions caused erythropoiesis to change from megaloblastic to normoblastic without other therapy. Subsequent administration of liver extract produced reticulocytosis only if the erythrocytes were less than 5 million. These results were attributed to the abolition of anemia anoxia. Because these findings were somewhat unexpected a similar study has been made and is the subject of this report.

The effects of transfusions of whole blood or packed erythrocytes sufficient to produce a normal hematocrit have been studied in four patients with untreated pernicious anemia. Bone marrow aspirations were studied before and after transfusion and after B_{12} therapy. In each patient erythropoiesis remained megaloblastic until B_{12} was given although in some instances a shift from early megaloblasts to more mature forms occurred. In every patient the absolute reticulocyte count decreased following transfusions. Subsequent administration of B_{12} produced a definite though small response in the reticulocytes. The peak of this response occurred in eight to ten days. One patient who received only 250 cc. of plasma before B_{12} had a normal reticulocyte response.

It is concluded that in these patients megaloblastic erythropoiesis was depressed by transfusions but normoblastic maturation did not occur without specific therapy.

RELATION BETWEEN THE ZONA RETICULARIS AND THE ZONA FASCICULATA OF THE ADRENAL CORTEX AND RENAL HEMODYNAMICS. *J. M. Little,* E. H. Yount and W. M. Kelsey.* Depts. of Physiology and Pharmacology, Medicine and Pediatrics, and the Laboratories of the A. H. Robins Co., Inc., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Inulin and PAH clearances were obtained in each of ten unanesthetized dogs on three days to establish control levels. The dogs then received daily intramuscular injections of ACTHAR-gel, 100 mg./M² for ten to twelve days, and the clearances were repeated between the fourth and twelfth day of administration. In twenty-nine determinations, each the average of three periods, the mean changes in function and the range compared to the controls were: C_{in}, +43.7 per cent (+6 per cent to +95 per cent); C_{PAH}, +52.4 per cent (−1 per cent to +117 per cent). Five dogs received rhothane (DDD) in daily oral doses of 14.5–200 mg./kg. for seven to sixty-six days. In fourteen determinations the mean changes from control and the range were: C_{in}, −21.5 per cent (+13 per cent to −44 per cent); C_{PAH}, −13.4 per cent (+16 per cent to −30 per cent). While continuing rhothane, ACTH administration was repeated. In nineteen determinations the mean changes from control and the range were: C_{in}, −3.2 per cent (+12 per cent to −19 per cent); C_{PAH}, +7.1 per cent (+42 per cent to −16 per cent). Four dogs received rhothane (200–300 mg./kg. for seven to fourteen days) and ACTH simultaneously. In ten determinations the mean changes from control and the range were: C_{in}, +16.5 per cent (+54 per cent to −5 per cent); C_{PAH}, +17.7 per cent (+39 per cent to −6 per cent). The animals remained in good health without special care. Autopsies showed no renal damage and varying degrees of adrenal atrophy confined to the inner two zones. Conclusion: Alterations of the level of function of the zonae reticularis and fasciculata affect the GFR and RPF in the dog without appreciably altering the electrolyte balance.

EFFECTS OF ACUTE ALTERATIONS IN CARBOHYDRATE METABOLISM ON THE NET SPLANCHNIC KETONE PRODUCTION IN MAN. *H. T. McPherson, E. E. Werk, F. L. Engel* and J. D. Myers.** Dept. of Medicine, Duke Univ. School of Medicine, Durham, N. C.

Utilizing hepatic venous catheterization, we have previously reported a technic for studying net splanchnic ketone production (NSKP) quantitatively in man before and after the intravenous infusion of sodium octanoate, a known ketone precursor. The present study concerns the effects on NSKP of acute alterations in carbohydrate metabolism in mildly ill males with non-metabolic illnesses, studied in the postabsorptive state.

Four groups of subjects were studied: (1) the control group receiving octanoate alone; (2) those receiving glucose mixed with octanoate; (3) those receiving glucose + insulin mixed with octanoate; and (4) a group studied three hours after a brief period of hypoglycemia.

Group	Basal	NSKP μm/min./M²	During Na Octanoate
Control (octanoate alone)	34 ± 5.20	158 ± 6.86	+124 ± 7.36
Glucose in octanoate	35.8 ± 6.60	106.3 ± 22.37	+70.5 ± 18.34
Glucose + insulin in octanoate	36.6 ± 12.06	125 ± 17.14	+88.4 ± 6.07
Three hours after hypoglycemia	160.7 ± 46.0	266.3 ± 43.5	105.6 ± 27.8

In both the glucose and glucose + insulin groups there was a statistically significant reduction in the increment of NSKP expected during octanoate infusion. Three hours after a brief period of hypoglycemia there was a markedly increased basal NSKP; however octanoate infusion induced no greater rise in NSKP than that of the control groups. The relationship of these quantitative findings to the so-called "Somogyi effect" noted clinically will be discussed.

EVALUATION OF RADIOSULFATE AS A MEASURE OF EXTRACELLULAR VOLUME IN EDEMATOUS PATIENTS. *L. L. Madison, H. C. Teng, D. W. Seldin,* A. F. Reid and R. MacDonald.* Depts. of Internal Medicine and Biophysics, Southwestern Medical School of The Univ. of Texas, Dallas, Tex.

To evaluate radiosulfate as a means of measuring extracellular volume in edematous states, three approaches were planned in order to circumvent lack of adequate reference standards: the time of diffusion equilibrium was empirically determined by comparing concen-

trations of S^{35} simultaneously in plasma, edema and ascites for fifteen hours; the validity of calculations of the S^{35} space was tested by comparing theoretic time curves of appearance of S^{35} in edema fluid with experimental curves; decrements in extracellular volume (diuresis or paracentesis) were compared with changes in radiosulfate space in the same subjects. Eleven edematous subjects were studied and eight restudied when edema-free.

Results indicate that radiosulfate is a suitable agent for measuring extracellular volume in edematous states for the following reasons: (1) mean time for diffusion equilibrium between plasma and ascitic fluid is 5.5 hours and between plasma and edema fluid is 11.3 hours; (2) mean changes in radiosulfate space from edematous state (24.8 L.) to edema-free state (11.4 L.) compared favorably with decrements in extracellular volume reflected by decreases in weight (13.6 kg.); (3) theoretic (derived from plasma data only) and experimental time curves of appearance of S^{35} into edema fluid were in excellent agreement.

SOME METABOLIC CHARACTERISTICS OF TUBERCULOUS ANIMALS. *S. P. Martin,* R. Green and C. D. Cooper.* Depts. of Medicine and Bacteriology, Duke Univ. School of Medicine, Durham, N. C.

Tissues of animals infected with Mycobacterium tuberculosis have a low succinic dehydrogenase activity and this can be restored by a nucleotide from normal tissue. The activity of this nucleotide can be duplicated by coenzyme A which has been treated with nitrous acid. This study deals with other metabolic effects noted in tuberculous animals.

Studies were carried out on the ability of infected animals to acetylate paraaminobenzoic acid. Control and infected guinea pigs were given 1 mg. of paraaminobenzoic acid and urine collected over a twelve-hour period. The free and acetylated derivatives were measured. The degree of acetylation in the control animals was 0.883 ± 0.037, in the infected animals 0.635 ± 0.075 mg. ($p < 0.02$). Studies were also carried out on non-protein sulfhydryl content of the tissues. The kidneys of infected animals have an elevated non-protein sulfhydryl content. Control values were 77 ± 3 mg. of glutathione per 100 gm. of tissue compared with 107 ± 9 ($p < 0.01$) for the infected animals.

It is suggested that these changes indicate disturbance in metabolism of high energy compounds and in protein synthesis which may account for part of the clinical picture of this disease.

MIXING IN BIOLOGICAL SYSTEMS. *G. R. Meneely.** Research Laboratory and Radioisotope Unit, Thayer V. A. Hospital, and Dept. of Medicine, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

A differential equation may be derived from the assumptions that the rate of mixing or disappearance of tracer substances is not only proportional to concentration but also inversely proportional to time. The integral of this equation is:

$$\text{Exponential form: } y = C_1 t^{-k}$$
$$\text{Log form: } \log y = -k \log t + \log C_1.$$

Since the tracer is already at a finite dilution when introduced the paradox of divergence of the time integral at zero time is resolved. This formulation or one derivative from it provides extraordinarily closely fitting curves to the most diverse sorts of biological mixing data such as the disappearance of radiopotassium from the blood of rats, of radiosodium from the blood of man, of radiobromine from the blood of the dog, of diiodotyrosine from the blood of the rat, of methenamine mandelate from the blood of man, and of helium mixing in the human lung. By double logarithmic plot it is easy to test whether given data may be fitted and the constants C_1 and k may be evaluated directly.

RELATIONSHIPS BETWEEN HALF-SECOND EXPIRATORY CAPACITY TEST AND LUNG VOLUMES AND INDEXES OF INTRAPULMONARY GAS DISTRIBUTION IN EIGHTY-FIVE PATIENTS WITH VARIOUS PULMONARY DISORDERS. *W. F. Miller, R. L. Johnson, Jr. and Nancy Wu (introduced by D. W. Seldin*).* Dept. of Internal Medicine, Southwestern Medical School of The Univ. of Texas, Dallas, Tex.

By plotting in a quadrantic system pulmonary stroke volume (estimated from vital capacity) and velocity air-flow (estimated from half-second expiratory capacity, 0.5 Sec. EC), precise expressions of the nature and extent of ventilatory insufficiency are obtained. By this method ventilatory defects were characterized as: obstructive (decreased velocity air-flow), restrictive (decreased pulmonary stroke volume), and combined. To examine the significance of ventilatory disturbances revealed by this analysis the anatomic extent of disorders was estimated

from residual volumes and total capacities, while their physiologic significance was estimated from indexes of intrapulmonary mixing. The obstructive group revealed normal or increased total capacities (TC = 133 ± 33 per cent) and residual volumes (RV = 149 ± 32 per cent). The restrictive group revealed decreased to normal TC (74 ± 11 per cent), and normal to increased RV (94 ± 29 per cent). The combined group showed normal to decreased TC (87 ± 14 per cent) and decreased to increased RV (136 ± 50 per cent), depending on the extent of the obstructive component. Thus classification of ventilatory defects by 0.5 Sec. EC tests correlates well with anticipated anatomic alterations in lung volumes. The 0.5 Sec. EC correlated excellently with the index of intrapulmonary mixing (r = 0.924). Thus velocity air-flow determines in part effective ventilatory gas exchange.

The classification of ventilatory disturbances by 0.5 Sec. EC test provides excellent insight into the anatomical nature of the disturbances as well as their physiologic significance.

TREATMENT OF HYPERTENSIVE EMERGENCIES WITH PARENTERAL RESERPINE. *J. H. Moyer,* W. M. Hughes, W. C. Daeschner, Jr. and E. W. Dennis.** Baylor Univ. College of Medicine, Houston, Tex.

Three groups of hypertensive patients were treated with reserpine by parenteral administration for periods varying from one to seventeen days: (1) severe, progressive, hypertensive cardiovascular disease (ten patients with malignant hypertension and four patients with severe, benign essential hypertension); (2) toxemia of pregnancy (six patients); and (3) acute glomerulonephritis in children (eight patients). The drug was administered at intervals of four to twenty-four hours either intravenously or intramuscularly in doses of 2.5 to 5 mg. in adults and 25 to 100 μg./kg. of body weight in children. The blood pressure response after administration of reserpine was characterized by a latent period of one to three hours following which the blood pressure usually decreased to normotensive or moderately hypertensive levels for a duration of two to twenty-four hours or longer. All of the patients except one obtained a significant reduction in blood pressure and 70 per cent became normotensive in the supine position. Excessive hypotension was rarely observed. Papilledema disappeared in seven of eleven patients, and hypertensive encephalopathy was relieved in four of six patients. It is concluded that parenteral reserpine is an effective and safe agent for the therapy of hypertensive emergencies.

ROLE OF FEMALE GENITAL FUNCTION IN CREATINE METABOLISM AS REVEALED BY THE SERUM CREATINE TOLERANCE TEST. *J. H. Peters,* R. Snyderman and J. C. Crutoher.* Investigative Medicine Service, V. A. Hospital, Atlanta, Ga.; Dept. of Medicine, Emory Univ. School of Medicine, Emory University, Atlanta, Ga.; and the Dept. of Research Medicine, Univ. of Pittsburgh School of Medicine, Pittsburgh, Pa.

The sex differences long-recognized in creatine metabolism have been indirectly explained by the demonstration that androgen therapy can suppress creatinuria in preadolescent boys and in disease states. However, since the female gonads might still be a factor in the maintenance of creatine intolerance in females, studies were undertaken using serum creatine tolerances. Normal females were compared with postmenopausal individuals and with patients previously subjected to ablation of ovarian and/or uterine function by surgery or radiation.

Results indicate that the relative creatine intolerance characteristic of the adult female is not affected by the presence or absence of functioning sex organs, but the findings do suggest that inability to dispose of exogenous creatine in serum increases with age independent of gonadal status. From these findings it may be concluded that androgen secretion in the male, rather than female sex function, is responsible for the well known difference in creatine metabolism.

FACTORS INFLUENCING PULMONARY COMPLIANCE IN HEART DISEASE. *W. W. Pryor, J. B. Hickam,* E. B. Page and H. O. Sieker.* Dept. of Medicine, Duke Univ. School of Medicine, Durham, N. C.

In congestive heart failure the lungs become stiff (low compliance). The role this change in pulmonary distensibility plays in producing cardiac dyspnea has stimulated considerable interest. However, little has been done to define the effect of pressure changes in the various partitions of the pulmonary vasculature and parenchymal alterations on compliance. Patients with mitral stenosis, apparent primary pulmonary hypertension, pulmonary stenosis and normal subjects receiving rapid infusions of albumin were studied to find some of the answers to this problem. Compliance is measured as: lung volume change (liters)/intraesophageal

pressure change (cm. H_2O) (normal .170 ± .05 lying).

Results revealed (1) "PC" pressure need not be elevated since subjects with apparent primary pulmonary hypertension had low compliance (e.g. average .090); (2) all patients with elevated pulmonary artery pressure had reduced compliance (e.g. mitral stenosis .075, pulmonary hypertension .090); (3) subjects with pulmonary stenosis have compliance values which are high normal (e.g. .205); (4) normal subjects have a fall in compliance following rapid infusion of albumin in amount sufficient to elevate central venous pressure 6–8 mm. Hg (e.g. control .123, after albumin .087).

Conclusions: (1) pulmonary hypertension is associated with stiff lungs; (2) elevation of "PC" pressure is not necessary for this change; and (3) permanent parenchymal changes need not be present.

Clinical Evaluation of Iron Turnover Studies. *C. E. Rath, R. Peterson and P. McCurdy (introduced by H. Jeghers*)*. Dept. of Medicine, Georgetown Univ. School of Medicine, Washington, D. C., and the National Inst. of Health, Bethesda, Md.

Following the studies of Huff on the rate of plasma clearance and red cell utilization of intravenously injected radioactive iron, there has been considerable dispute regarding the clinical value of such studies. The present report deals with a clinical evaluation of plasma and red cell radioiron turnover in twenty patients (twenty-eight turnovers) and a comparison of the findings with those in fifteen normal adult males and females.

The patients studied included iron deficiency, refractory anemia, anemia of Addison's disease, hemochromatosis, a variety of hereditary hemoglobin abnormalities, aplastic anemia, myeloid metaplasia, uremia, cirrhosis and acquired hemolytic anemia.

It is concluded that iron turnover rate studies, when properly interpreted, give valid information regarding marrow function and red cell destruction and that the information thus obtained is of value in selecting patients for splenectomy and in the diagnosis of certain obscure anemias. Calculations of value include the metabolic iron pool size, number of pools turned over per day, mg./Fe turned over per day, per cent and rate of incorporation of RaFe into circulating red cells, and per cent red cell mass turned over per day. Substantiating data will be presented.

Biologic Decay Rates and Excretion of Radiocesium, Cs^{134}, in Dogs. *C. T. Ray,* G. E. Burch* and S. A. Threefoot.** Tulane Univ. School of Medicine, New Orleans, La.

Aspects of cesiokinetics were studied with Cs^{134} in three dogs observed continuously under metabolically controlled conditions for forty-seven days. Cl^{35}, Na^{23} and K^{39} were studied simultaneously. The data indicated: (1) 0.4 to 0.8 of Cs^{134} in the plasma was transferred per minute to the extraplasma compartments and 0.04 to 0.06 of that in the extraplasma compartments returned to the plasma per minute. (2) Half of the injected tracer was excreted in the urine and stools in seventeen to thirty-nine days, twenty-seven to forty-six days being required to excrete half in the urine alone. From 50 to 55 per cent of the injected dose was recovered in urine, 8 to 14 per cent in stools, 8 to 37 per cent remaining in the body. (3) At no time was equilibrium of distribution reached. (4) Rates of urinary clearance of Cs^{134} varied from 43 to 57 per cent of K^{39}. (5) Cs^{134} is not as satisfactory a tracer of K^{39} as is Rb^{86}.

Coronary Blood Flow and Myocardial Carbohydrate Metabolism in Mitral Stenosis. *J. L. Read, R. R. Porter* and S. C. Bradford.* Cardiovascular Section of the Medical Service and Cardiovascular-Pulmonary Research Laboratory, McGuire V. A. Hospital, and the Cardiovascular Div. of the Dept. of Medicine, Medical College of Virginia, Richmond, Va.

In six patients with advanced mitral stenosis, the coronary blood flow was measured using the technic of coronary sinus catheterization and the nitrous oxide method of Kety and Schmidt. Cardiac output was determined by the Fick principle. In addition, direct analyses were made of the coronary A-V differences of oxygen, glucose, lactate and pyruvate.

The coronary blood flow was reduced in all cases, with a range of 57 to 74 cc./100 gm./min. compared to the normal range of 91 to 103 cc./100 gm./min. The coronary A-V oxygen difference varied from 9.5 vol. per cent to 15.38 vol. per cent compared to the normal range of 10.00 to 12.00 vol. per cent. The cardiac index in the six cases was reduced, with a range of 1.36 to 3.93 L./min./M^2 and a mean of 2.35. The mean coronary glucose A-V difference was 5.5 mg. per cent compared to the normal of 2.66 mg. per

cent. The mean coronary lactate A-V difference was 1.93 mg. per cent and the mean coronary pyruvate A-V difference was 0.65 mg. per cent, essentially normal values.

The significantly reduced coronary blood flow indicates either a reduced requirement for coronary blood flow or an inability to maintain a normal coronary flow because of the stenotic mitral valve. Since the reduction in coronary blood flow correlated with the reduction in cardiac index, with the increase in the coronary oxygen A-V difference and with the calculated left ventricular efficiency, it would appear that the latter is the most likely explanation. Because of the reduced coronary blood flow, adaptive mechanisms apparently allow a greater extraction of glucose than normally occurs with a given arterial glucose level.

ACUTE EFFECTS OF MERCUHYDRIN ON CARDIAC OUTPUT AND URINARY EXCRETION. *A. Ruskin (introduced by R. Gregory*)*. The Univ. of Texas Medical Branch, Galveston, Tex.

Right intracardiac pressures have been found by Lenègre to decline right after mercurial administration, indicating a possible immediate improvement in cardiac output *before* its direct renal effects in heart failure.

Twelve patients were given 2 cc. of mercuhydrin intravenously. Two fifteen-minute control periods were compared to three fifteen-minute postdrug periods. In seven subjects not in heart failure urine sodium and chloride (mEq./min.) rose rapidly in all. Urine potassium rose in three, but fell later below control levels in six cases. Urinary volume rose significantly in four patients. Venous pressure varied irregularly. Cardiac output (ballistocardiographic) rose immediately in four cases (excitement?) but declined (later especially) in six, remaining unchanged in one. Five heart failure patients all showed rapid rises in sodium, then chloride and water excretion, a rise in potassium excretion in four cases and a fall in one case. Venous pressure fell rapidly in four patients, and was unchanged in one; later ascended in two. Cardiac output fell early in three cases, but rose *after* diuresis in four of five patients above control levels.

The results reaffirm the *primary* renal mechanisms of mercurial diuresis, and the *secondary* cardiac effects.

EFFECT OF HEXAMETHONIUM-INDUCED GANGLIONIC BLOCKADE ON RENAL FUNCTION IN PATIENTS WITH CONGESTIVE HEART FAILURE. *H. W. Schnaper, R. D. Kovach and E. D. Freis.** V. A. Hospital and the Georgetown Univ. Hospital, Washington, D. C.

The improvement in cardiovascular function recently reported by Kelley, Freis et al. and Brodh and coworkers following administration of ganglionic blocking agents to patients in congestive heart failure prompted the current investigation into the physiologic changes in renal function in patients in congestive failure in response to acute doses of hexamethonium. It was found in eight control studies that renal plasma flow (RPF) was diminished and glomerular filtration rate (GFR) proportionately less diminished in the subjects with congestive failure, resulting in an increased filtration fraction (FF). After intravenous dosage of hexamethonium sufficient to cause ganglionic inhibition, as measured by sustained diminution in blood pressure and mydriasis plus conjunctival injection, both GFR and RPF decreased in four cases in the first fifteen to thirty minutes, with little resultant change in FF. After this initial drop, and despite continued inhibition of the ganglionic impulses, RPF and GFR both returned to control values or above, keeping FF relatively unchanged. In four cases there was no drop in RPF and GFR after hexamethonium injection, and in two cases the rebound values exceeded the control values.

These data are at odds with those reported by Brodh and coworkers who found a significant increase in RPF in congestive failure patients following blockade with dibenzylene.

SPECIFIC THERAPY FOR SALICYLATE POISONING. *G. E. Schreiner, L. B. Berman, J. Griffin and J. Feys (introduced by L. H. Kyle*)*. Dept. of Medicine, Georgetown Univ. Hospital, Washington, D. C.

Salicylates account for 4 per cent of fatal poisonings due to solids and liquids in the United States. Surprisingly little data are available on fatal dosages, blood levels, distribution of salicylate, protein binding, etc. There has been no specific therapy. Abel in 1913 removed salicylate from animals by vividiffusion. Doolan et al. reported removal of some salicylate from a human during one hour of dialysis. Successful dialysis has not been reported.

This report concerns a patient who ingested 210 gm. of aspirin and was comatose with hyperthermia, hyperpnea, ketosis, absent corneal reflexes and a blood salicylate level of 90 mg. per

cent. Dialysis resulted in rapid clinical and chemical recovery. Hypoprothrombinemia did not become normal until forty-eight hours after the salicylate level was zero.

Preliminary calculations derived a volume of distribution for salicylate compatible with extracellular fluid. Studies of protein binding showed no interference with dialysis. The clinical course is compared with a patient who ingested a smaller amount of aspirin but had a similar blood level and was treated supportively. The amount of salicylate recovered in the bath in six hours in Case 1 exceeded that recovered in the urine in 144 hours in Case 2.

ANTIHYPERTENSIVE EFFECT OF METAL BINDING AGENTS. *H. A. Schroeder,* H. M. Perry, Jr. and E. M. Menhard.* Hypertension Div., Dept. of Internal Medicine, Washington Univ. School of Medicine, St. Louis, Mo.

Non-neurogenically acting antihypertensive agents (thiocyanate, nitroprusside, azide, hydrazinophthalazines, mercaptans) have in common an affinity for transition and nearby metals. Therefore, 5 mg. each of a series of nine disodium ethylenediamine tetraacetates (EDTA) of increasingly tightly bound divalent metals was assayed for vasoactivity in groups of normotensive and renal hypertensive rats, blood pressure being recorded on a Sanborn electromanometer. The significant changes occurred in hypertensive but not normotensive animals, mean diastolic pressure being depressed 30, 42, 28, 43, 60 and 50 mm. Hg by hydrogen, calcium, manganous, chromous, ferrous and cobaltous chelates, respectively, and less than 20 mm. by zinc, cupric and nickelous chelates. Vasoactivity became negligible when the log K_2 of the chelate exceeded 16.5, indicating tight binding. Similar differential effects were observed with the tetrahydrogen and lesser with the magnesium chelates while the ferric was pressor. A polyaminocarboxylic acid and 8-hydroxy quinoline were likewise depressor only in hypertensive rats. Zinc, ferrous and manganous ions as chlorides were relatively inert, nickelous was pressor and cobaltous differentially depressor. No marked effect was observed after oral or parenteral calcium or magnesium EDTA in hypertensive patients. These results are consistent with the *in vivo* binding of metal, the logs K_2 of which approximate 16.5 for EDTA.

CEREBRAL CIRCULATORY EFFECT OF THE ADMINISTRATION OF 3 PER CENT CO_2 TO SUBJECTS WITH CHRONIC PULMONARY INSUFFICIENCY. *W. Sensenbach, L. Madison and S. Eisenberg (introduced by E. S. Sulkin*).* Dept. of Internal Medicine, Southwestern Medical School of The Univ. of Texas, and the Dept. of Medicine, V. A. Hospital, Dallas, Tex.

CO_2 3 per cent, O_2 21 per cent, CO_2 3 per cent, and O_2 97 per cent were administered to fourteen subjects with chronic pulmonary insufficiency. Arterial O_2 saturation, pCO_2 and pH were determined before and after, CBF at the end of, each breathing period.

Administration of 3 per cent CO_2, 97 per cent O_2 significantly changed CBF (47 per cent increase) and CVR (25 per cent decrease); CBF, CVR were unaltered by 3 per cent CO_2, 21 per cent O_2; CMR O_2, CMR glu. did not change with either mixture. Arterial O_2 saturation increased (86–93 per cent) with 3 per cent CO_2, 21 per cent O_2 and 3 per cent CO_2, 97 per cent O_2 (82–100 per cent). pH did not change with either mixture. The most striking finding was the unexpectedly small rise in arterial pCO_2 after inhalation of the CO_2 mixtures, when compared to the marked hypercapnea produced with 100 per cent O_2.

The findings suggest that cerebral circulatory changes accompanying administration of high oxygen mixtures to subjects with chronic pulmonary insufficiency are more intimately related to changes in arterial O_2 saturation than to changes in blood pH or pCO_2. The slight rise in arterial pCO_2 despite administration of CO_2 loads suggests the existence of chemoreceptors in the lung sensitive to increased CO_2 tension of inspired air.

TREATMENT OF POSTURAL HYPOTENSION WITH A COUNTERPRESSURE GARMENT. *H. O. Sieker, J. B. Burnum, J. B. Hickam* and K. E. Penrod.* Dept. of Medicine, Duke Univ. School of Medicine, Durham, N. C.

Postural hypotension may be a severe disabling illness which is difficult to treat. Experimentally, counterpressure to the lower half of the body will prevent symptoms. For this purpose a garment has been developed which consists of tailored graded-pressure nylon-elastic knit trousers that apply 15 to 20 mm. Hg pressure.

To study the hemodynamic effects of this garment, an air-filled full-pressure anti-g suit which applies a similar pressure was used on eight postural hypotensive patients. Arterial

pressure, cardiac output and pulmonary arterial pressure were determined while supine and erect, unprotected and protected. The suit alleviated the symptoms including syncope which occurred with standing. The average fall of mean arterial pressure with tilt was 45 mm. Hg unprotected and 8 mm. Hg protected. With tilt the average decrease in cardiac output was 46 per cent without counterpressure and 21 per cent with counterpressure. The mean pulmonary arterial pressure fell 6–8 mm. Hg with release of counterpressure while standing. This evidence indicates that the pressure suit is effective by increasing peripheral arterial resistance and venous return to the heart.

Individually tailored elastic garments have been used in three of the severest cases of postural hypotension for twelve to twenty-two months. The suit has been practical and successful in returning these patients to useful activity.

ELECTROMAGNETIC MEASUREMENT OF BLOOD FLOW THROUGH INTACT HUMAN ARTERIES. *M. P. Spencer, A. B. Denison, Jr., W. F. McGuire and R. T. Myers (introduced by H. D. Green*).* Depts. of Physiology and Pharmacology, Urology and Surgery, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Measurements of blood flow through intact blood vessels has been made practical by a recent development of the electromagnetic method of flow recording. The sources of instability of previous systems have been considerably reduced by use of a square-wave magnetic field and an AC amplifier containing a chopping circuit to eliminate electrode voltages induced during reversal of the magnetic field.

The unit applied to the blood vessel consists of a small U-shaped electromagnet imbedded in plastic with a slot at the open end to accommodate the vessel and provided with two stainless steel electrodes. The size and shape of this magnet electrode assembly is altered to meet the particular application. The vessel unit can be sterilized and is easily applied. The sensitivity of each unit, determined by *in vitro* calibrations of blood forced through an artery or vein, is linear and constant.

To date the meter has been applied to the renal artery in four instances of nephrectomy and to the femoral artery during replacement of a thrombosed segment with a vein graft. These and other applications will be discussed.

THE ANEMIA OF UREMIA: HEMOLYTIC STATE MEASURED BY THE RADIOCHROMIUM METHOD. *D. A. Sutherland, S. McCall, F. Jones and E. E. Muirhead.** Radioisotope Unit, Dallas V. A. Hospital, and the Depts. of Medicine and Pathology, The Univ. of Texas Southwestern Medical School, Dallas, Tex.

The anemia of chronic uremia was studied in eleven patients by means of the autotransfusion of CR^{51} tagged RBC. Two patients revealed normal RBC survival indicating a bone marrow dysfunction only. The RBC survival was significantly lowered in the remaining nine patients as indicated by the following values (in days) for the mean life-span: twenty-five, thirty, thirty, thirty, thirty-five, forty, forty-five and fifty-five (normal values eighty to ninety days). In two cases the same shortened life-span obtained by autotransfusion was detected by transfusion of tagged RBC from the uremic patients into normal subjects. The transfusion of normal RBC into one of these patients yielded a normal life-span.

Four normal dogs were subjected to bilateral nephrectomy and no dialysing procedure. Four days later the RBC from the uremic animals were tagged with Cr^{51} and transfused into normal dogs. The mean life-span of these RBC was fifteen days (normal eighty to ninety days).

The anemia of uremia in most of these examples resulted in part from a hemolytic state due apparently to alterations of the RBC. Indications for a bone marrow dysfunction were also noted.

ACUTE EFFECT OF HEPARIN ON CEREBRAL BLOOD FLOW AND CEREBRAL METABOLISM. *R. W. Talley (introduced by P. L. Day*).* Dept. of Medicine, Univ. of Arkansas School of Medicine, Little Rock, Ark.

Studies of the cerebral blood flow (CBF), cerebral oxygen utilization ($CMRO_2$), cerebral vascular resistance (CVR), and cerebral glucose utilization (CMRG) were made before and after a large dose of heparin in eleven aged patients. All of these patients were in a state hospital for nervous and mental disease and had varying degrees of mental deterioration apparently due to cerebral arteriosclerosis.

There was no correlation between degree of mental deterioration and the rate of CBF. Forty-eight to seventy-two hours after the control study the patient was given 200 mg. of heparin intravenously. Three hours after the

administration of the heparin a repeat cerebral blood flow study was made. The studies before and after the administration of heparin were compared and no statistical difference in the CBF, $CMRO_2$, CVR and CMRG was found. The average values of the CBF, $CMRO_2$, CVR and CMRG before and after heparin were as follows:

	CBF	$CMRO_2$	CVR	CMRG
Before	33.8	2.2	3.4	4.5
After	33.1	2.0	3.4	4.2

INFLUENCE OF THIOURACIL AND METHIMAZOLE ("TAPAZOLE") ON THYROID FUNCTION IN DOGS WITH SPECIAL REFERENCE TO SERUM CHOLESTEROL CHANGES. *S. Y. Tsai, L. G. May, V. A. Stembridge and R. Gregory** (with the technical assistance of A. Bennett, M. Kobayashi, M. Finley and J. R. Bateman). John Sealy Memorial Laboratory and Dept. of Internal Medicine and Pathology, Univ. of Texas Medical Branch, Galveston, Tex.

It has been suggested that the hypercholesterolemia in dogs receiving thiouracil may be due to a specific effect of the drug on serum cholesterol rather than to its antithyroid action. The absence of hypercholesterolemic effect of methimazole when given in a single daily dose would seem to support this hypothesis. The present study is designed to clarify these points.

Fifteen healthy mongrel dogs were divided into three groups: (1) no medication, (2) thiouracil in a single daily dose for two to three weeks and (3) methimazole five doses per day for three weeks. Serum cholesterols, PBI, histologic changes and thyroid I-131 uptakes were studied. Hypercholesterolemia and depression of thyroid I-131 uptake was observed in groups 2 and 3 but not in group 1. Serum PBI was found to normally low (Barker's method) and showed no significant change after the administration of thiouracil or methimazole. Histologic studies are in progress.

As hypercholesterolemia induced by thouracil and methimazole (in daily divided doses) correlates with decreased thyroid I-131 uptake, it is concluded that thiouracil does not have a specific effect on serum cholesterol and that hypercholesterolemia is a manifestation of induced hypothyroidism. The significance of normally low PBI in dogs will be discussed.

THE PERMEABILITY OF CAPILLARIES TO LARGE MOLECULES. *K. Wasserman and H. S. Mayerson.** Dept. of Physiology, Tulane Univ. School of Medicine, New Orleans, La.

This study of capillary permeability to large molecules was stimulated by observations of transudation from the circulation of infused plasma and normal saline solutions containing relatively large molecular weight solutes. We have followed the rates of disappearance of large molecules from plasma and their appearance and concentration in thoracic duct lymph. The leakage of larger molecules from plasma and their appearance in lymph is inversely related to their molecular weight when plasma volume and rate of plasma transudation are constant. Even relatively large molecules (dextran—average M. W. = 412,000) get into lymph, albeit in small amounts. The plasma-lymph gradients are influenced markedly by the size of the infusion volume. When the ratio of infusion to plasma volume is large, the plasma-lymph concentration gradient of all large molecules in circulation falls and the lymph flow increases regardless of the type of colloidal solution involved. This indicates that the permeability of the capillary wall to albumin, globulin and all large molecules is increased. The decreased gradient is the result not only of a fall in plasma but a rise in lymph solute concentration. These results are interpreted in terms of the pore theory as signifying a stretching of the capillary wall pores consequent to high capillary pressure from the increased volume in the circulation.

Case Reports

Retroperitoneal Pneumography in the Diagnosis of Retroperitoneal Lymphomatous Neoplasms*

RALPH M. MYERSON, M.D. *and* GEORGE T. WOHL, M.D.
Philadelphia, Pennsylvania

THE diagnosis and demonstration of retroperitoneal lymphomatous neoplasms is a serious and difficult problem. In most such cases physical examination, laboratory tests and conventional roentgenologic studies are unrevealing.

We have found retroperitoneal pneumography induced by the presacral insufflation of air to be a useful adjunct in the demonstration of retroperitoneal Hodgkin's disease and leukemic nodes when other diagnostic methods have failed. This procedure has provided valuable diagnostic and prognostic information with a minimum of discomfort and risk to the patient and has been of value in selection of the type of therapy.

TECHNIC

The technic of presacral air injection is not difficult. With the patient in the knee-chest position, the skin just distal and to one side of the tip of the coccyx is cleaned and infiltrated with a local anesthetic. A 3 inch, 16 gauge needle is directed obliquely upward, inward and forward under the coccyx in such a manner that its point comes to rest in the presacral, retrorectal fatty areolar tissue. An examining finger is kept in the rectum to insure proper position of the needle. The usual technic has been modified by the use of an 18 inch length of No. 50 polyethylene tubing which is threaded through the needle. The latter is removed and the tube strapped to the patient. Using a 50 cc. syringe, three-way stopcock and an adaptor fitted to the tubing, air is injected under fluoroscopic guidance. The polyethylene tubing makes it possible to give the injection conveniently and facilitates positioning of the patient so that an adequate amount of air is delivered in the desired location. About 1,000 cc. has been required for the average patient.

Routine stereoscopic frontal and single lateral roentgenograms are obtained as soon as possible after the injection. In addition, body section films of the upper and lower retroperitoneal areas are taken. When involvement of one side in particular is suspected, better delineation may be obtained if the roentgenograms are repeated after the patient has rested on the opposite side for twenty to thirty minutes. Some degree of mediastinal emphysema is present in some patients after several hours in the upright position, and in several cases this has been sufficient to obtain satisfactory mediastinal pneumograms.

No complications have been noted in a series of twenty patients studied in this manner. Transient abdominal and subdiaphragmatic discomfort has been present in most patients. Air embolism is apparently rare, only one such catastrophe (and that non-fatal) having been reported.[1] Mosca reviewed 1,500 cases in which retroperitoneal pneumography was performed without serious complication.[2] Because of its rapid absorption and probable greater margin of safety, oxygen has been used by most operators. Air has the advantage of being more conveniently administered and with its use there is a better possibility of outlining the mediastinum.

* From the Departments of Radiology and Medicine, Veterans Administration Hospital, Philadelphia, Pa.

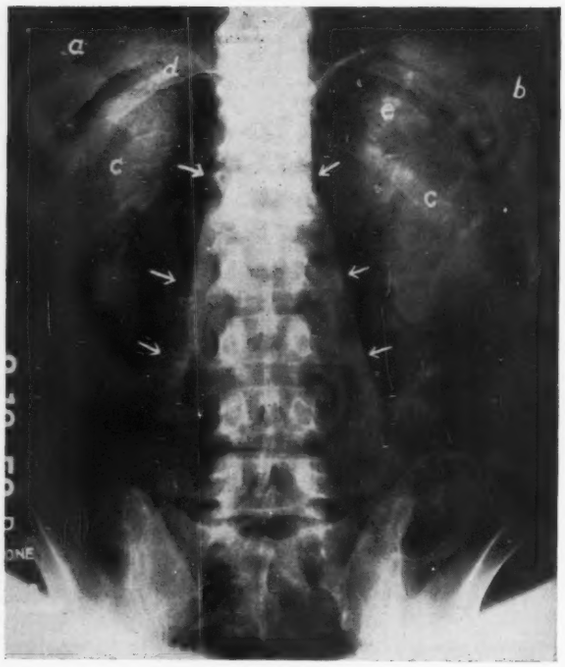

FIG. 1. Anteroposterior Bucky film of normal retroperitoneal pneumogram: *a*, liver; *b*, spleen; *c*, kidneys; *d*, right adrenal gland; *e*, left adrenal gland. Arrows indicate appearance of the normal psoas musculature and midline retroperitoneal structures.

Figure 1 demonstrates a normal retroperitoneal pneumogram. In addition to excellent delineation of the kidneys, adrenal glands, liver and spleen, the normal width and general appearance of the psoas muscles and midline retroperitoneal area is demonstrated.

The following typical cases are presented in which retroperitoneal pneumography was of value in the demonstration of retroperitoneal lymphomas.

CASE REPORTS

CASE I. J. R., a thirty year old white man, had had Hodgkin's disease since 1949, manifested by recurrences of cervical lymph node enlargement. He had been treated by both x-ray and nitrogen mustard with temporary remissions. His last course of therapy had been given eight months prior to admission, following which he had been well for about seven months. One month prior to entry persistent backache and malaise developed and on June 26, 1953, he was admitted to the Veterans Administration Hospital in Philadelphia. Physical examination, laboratory tests and routine roentgenographic studies, including an intravenous urogram, were unrevealing. Retroperitoneal pneumography (Fig. 2) revealed a large midline mass. X-ray therapy to the back gave prompt symptomatic improvement.

CASE II. E. B., a forty-two year old Negro man, had had chronic lymphatic leukemia since 1950. Therapy had consisted of local x-ray, nitrogen mustard and triethylene melamine. He was admitted to the Veterans Administration Hospital on October 5, 1953, with a one-month history of fatigue, leg cramps and abdominal swelling.

Physical examination revealed generalized lymphadenopathy and a moderate degree of ascites. The white blood cell count was 33,000 per cu. mm., of which 80 per cent were mature lymphocytes, 5 per cent lymphoblasts, 10 per cent smudge cells and 5 per cent polymorphonuclear leukocytes. The remainder of the laboratory studies were negative except for a moderate anemia. Roentgenograms of the chest revealed bilateral hilar lymphadenopathy. Gastrointestinal x-rays and an intravenous urogram were negative. The routine abdominal roentgenogram and stereoscopic frontal views of the abdomen after retroperitoneal pneumography were interpreted as being within normal limits. Laminagrams of the lower retroperitoneal area, however, revealed significant nodal enlargement. (Fig. 3.) Whole body x-ray therapy produced dramatic improvement in all respects and the patient was asymptomatic and had a normal hemogram when last seen in July, 1954.

CASE III. J. D., a twenty-eight year old white man, had had Hodgkin's disease since 1952, manifested initially by cervical lymphadenopathy. Therapy with nitrogen mustard and x-ray had produced remissions.

In February, 1954, the patient was admitted to the Veterans Administration Hospital in Philadelphia with complaints of pain in the lumbar region, fever and malaise. Retroperitoneal involvement was suspected but physical examination, laboratory tests, conventional roentgenograms and retroperitoneal pneumography were negative. Symptoms persisted and a repeat presacral air study in July, 1954, revealed a definite mass. (Fig. 4.) Localized x-ray therapy is contemplated.

CASE IV. J. C., a forty-one year old white man, had had Hodgkin's disease since 1951, initially manifested by cervical lymphadenopathy. Therapy had consisted of x-ray therapy and nitrogen mustard. The patient had been well for a period of two and a half years, follow-

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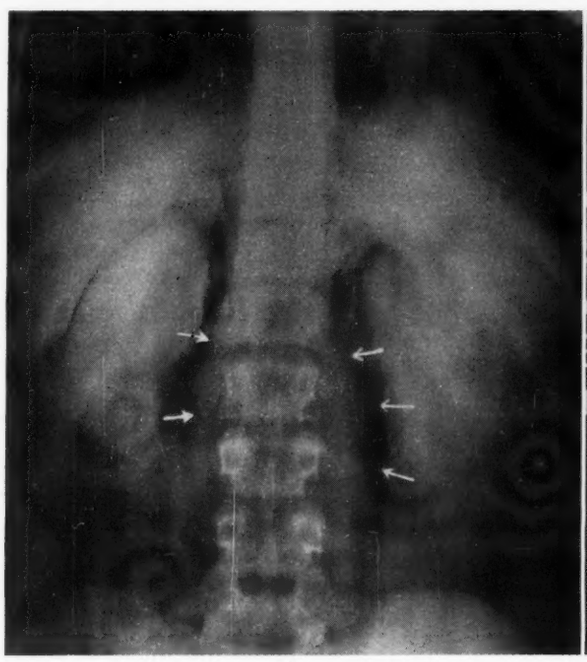
FIG. 2. Case I, J. R. Hodgkin's disease. Anteroposterior Bucky film in which arrows indicate large retroperitoneal mass.

FIG. 3. Case II, E. B. Chronic lymphatic leukemia. Laminograhic study of lower midline retroperitoneal area following pneumography. Arrows indicate enlarged nodal masses.



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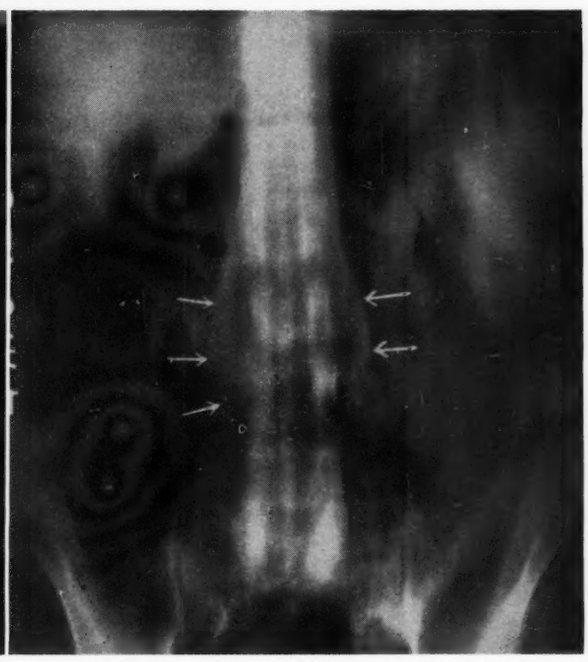

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FIG. 4. Case III, J. D. Hodgkin's disease. Laminographic study following retroperitoneal pneumography showing midline retroperitoneal mass.

FIG. 5. Case IV, J. C. Hodgkin's disease. Laminographic study following retroperitoneal pneumography. Arrows indicate retroperitoneal mass.

ing which weakness, cough, dyspnea and pain in the back developed. He was admitted to the Veterans Administration Hospital in Philadelphia with these complaints on August 13, 1954. Physical examination at this time revealed pallor, malnutrition, generalized lymphadenopathy and splenomegaly. Laboratory studies were not remarkable except for a moderate anemia. Roentgenogram of the chest revealed large mediastinal nodes. Other roentgenographic studies, including an intravenous urogram, were normal. Body section films after retroperitoneal pneumography revealed a midline retroperitoneal mass in the lumbar region. (Fig. 5.) The patient is being treated with nitrogen mustard.

Air has been utilized in roentgenology for many years as a means of contrast to differentiate tissues and organs situated in media of homogeneous density. In 1921, Carelli[3] introduced air into the renal fascia to outline the kidneys and adrenals. Following the work of Ruiz Rivas[4,5] the presacral technic for production of retroperitoneal pneumography gradually supplanted perirenal insufflation. Numerous articles have been published attesting to the value of this procedure for the demonstration of abnormalities of the kidneys and adrenal glands.

Retroperitoneal pneumography is well suited for the demonstration of midline retroperitoneal neoplastic masses. It must be emphasized that a negative study does not rule out the presence of pathologic changes. Recent experience with its use in the demonstration of metastatic nodes from testicular tumors would seem to indicate that retroperitoneal pneumography will not satisfactorily demonstrate lesions less than 4 cm. in diameter.[6]

SUMMARY

Retroperitoneal pneumography is a valuable adjunct in the diagnosis and demonstration of retroperitoneal lymphomatous neoplasms.

Modification of the usual technic by the use of a polyethylene catheter for administration of the gas is recommended. Fluoroscopy and body section roentgenography are believed to be important additions to the usual roentgenographic technic.

Four typical cases are presented in which retroperitoneal pneumography was helpful in the demonstration of retroperitoneal lymphomatous masses.

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Rupture of Aortic Aneurysm into the Pulmonary Artery*

Report of a Case Proved by Cardiac Catheterization

DAVID BUTTROSS, JR., M.D. *and* JOHN SALATICH, M.D.

Lake Charles, Louisiana *New Orleans, Louisiana*

NUMEROUS cases of rupture of an aortic aneurysm into the pulmonary artery have been reported in the literature during the past decade or so, and the clinical picture produced by this event has been adequately described so that at least a presumptive antemortem diagnosis can be made in many cases.[1–6] There is, however, only one report in which the diagnosis was proved by cardiac catheterization.[2] The purpose of this report is to add another such case and discuss the diagnosis and pathophysiology of this condition.

Up to the present, eighty-five cases of aortic aneurysm with rupture into the pulmonary artery have been reported.[1–6] Only seven were diagnosed before death. During the past year two cases were diagnosed at this hospital; one antemorten (case reported herein), the other postmortem.

The great majority of aneurysms of the thoracic aorta are in the ascending portion, and in view of the intimate relationship of the pulmonary artery to the ascending aorta one wonders why there is not a greater incidence of rupture into this vessel.

The onset of this disorder may be very acute, with extreme dyspnea, cough and precordial pain. Rarely the patient is relatively asymptomatic, complaining of mild to moderate dyspnea. The subsequent course is probably dependent in part on the size of the fistula. The patient may have progressive signs of right heart failure. The pulse pressure is wide and other peripheral arterial signs typical of aortic insufficiency are present. A systolic or continuous thrill is felt over the pulmonic area, and a continuous machinery-like murmur with systolic accentuation is heard over the same area. X-ray of the chest usually reveals evidence of aneurysm of the thoracic aorta and occasionally a prominent pulmonary conus, the latter sometimes being obscured by the aneurysm. The electrocardiogram usually reveals right axis deviation or right ventricular hypertrophy.

Patients with this disorder may die suddenly with the onset of the rupture or live for days or months, the average duration of life being three to four weeks. The longest survival time recorded is four years, reported by Clerc.[7] This, however, is very unusual, and there is some question as to the time of onset in this case.

This condition is most frequently misdiagnosed as aortic insufficiency but several points may be kept in mind to guard against this error. The continuous character of the murmur is in marked contrast to the to-and-fro murmur of aortic insufficiency. In the electrocardiogram right axis deviation is the rule, while in aortic insufficiency left axis deviation with left ventricular hypertrophy is characteristic. The peripheral arterial signs are the same in both conditions. Increased pulsation of the pulmonary artery is frequently seen in cases of aortic-pulmonary fistula whereas in cases with aortic insufficiency there is prominent pulsation of the aorta. The aortic second sound is present in the former but tends to be absent in the latter condition.

Patent ductus arteriosus enters into the differential diagnosis. A negative past history of cardiac symptoms or signs is helpful. The onset is not nearly as abrupt or drastic in patent ductus as in the acquired communication, and positive serologic reactions for syphilis and evidence of aortic aneurysm favor the diagnosis of acquired aortic-pulmonary fistula. The machinery-like murmur is characteristic of both conditions.

* From The Department of Medicine, Louisiana State University School of Medicine and Charity Hospital, New Orleans, Louisiana.

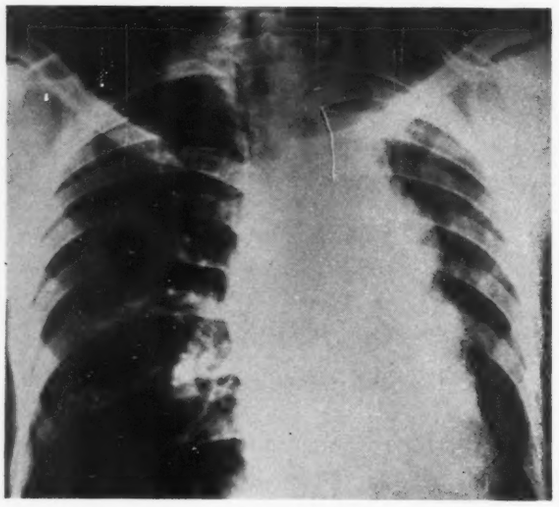

FIG. 1. Dilatation of the aortic arch, prominence of the pulmonary artery and moderate left ventricular enlargement.

Rupture of the sinus of Valsalva into the pulmonary artery, right ventricle or right auricle may give signs and symptoms practically identical with those of aortic aneurysm with rupture into the pulmonary artery.[8–10] Absence of radiologic aortic aneurysm and negative serologic tests for syphilis favor the diagnosis of rupture of the sinus of Valsalva.

Why is there evidence of right heart strain in patients with this condition, while in patients with patent ductus arteriosus left heart strain is evident? This is probably due to long-standing pressure of the aneurysmal sac on the pulmonary artery prior to rupture, with resultant increased resistance distal to the pulmonary valve and right ventricular strain.[1,2] Another theory as regards right heart strain is based on the direction of blood flow from the shunt.[1] If the jet of blood is directed away from the pulmonic valve, there is little increased resistance to right ventricular outflow; however, if the jet is directed at a right angle to the pulmonary artery or towards the pulmonic valve, a definite increase in resistance to outflow occurs.

CASE REPORT

F. B., a fifty-two year old Negro dock laborer, was admitted to Charity Hospital on November 13, 1952, with a chief complaint of dyspnea of ten days' duration. He stated that about one month before admission he was struck on the right shoulder by a loading machine. At this time he noticed some aching but the skin was not broken. The next day he noticed a small

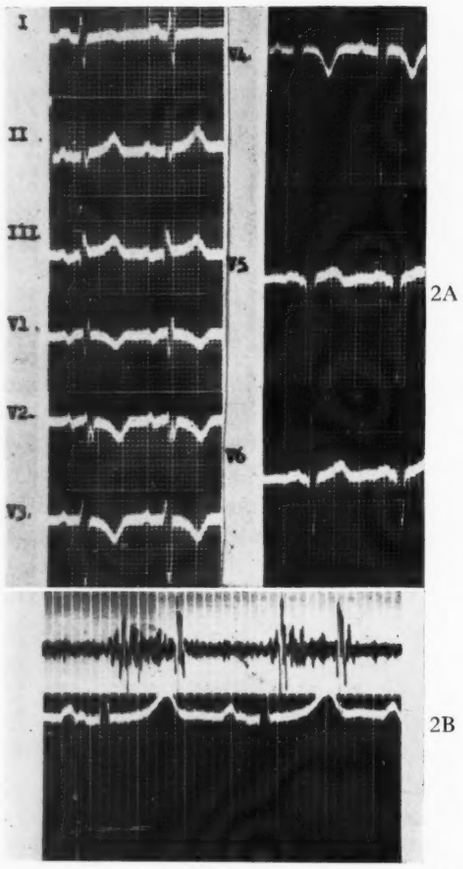

FIG. 2. A, note the right axis deviation. B, the phonocardiogram shows a continuous murmur with a systolic accentuation.

protrusion above the right clavicle which would appear when he lay down and disappear when he sat up. He attributed this protrusion to the injury but paid no particular attention to it since it caused him no discomfort. About ten days before admission he began to notice severe weakness, dyspnea, cough and swelling of the feet. The dyspnea became progressively worse, and the cough productive of a white, foamy sputum. Hoarseness also developed.

There appeared to be no pertinent data in the past or family history.

Physical examination revealed a moderately dyspneic, middle-aged colored man who did not appear acutely ill. Blood pressure was 170/90, equal in both arms, pulse was 104 and regular, respiration rate 20. Pertinent abnormalities included the following: Above the right clavicle there was a soft, round mass which was easily reducible by pressure and which increased in size on coughing. This was believed to be a pleural hernia related to the injury of the previous month. The apex beat was in the

seventh interspace outside the anterior axillary line, forcible and diffuse. There was dullness to the left of the sternum in the second and third interspaces, and a systolic thrill was present in this region. A loud, harsh, continuous murmur with systolic accentuation was audible over the left upper chest, loudest in the second left interspace near the sternum. There were no rales in the lungs. The liver was palpable five fingerbreadths below the rib margin and somewhat tender. The spleen was not palpable. There was moderate edema of the feet and ankles. Blood picture and urinalysis were normal. Complement fixation test for syphilis was positive, the quantitative Kahn test was 8 units. Venous pressure in the right arm was 130 mm. of water, in the left 160.

Fluoroscopy revealed what was interpreted as dilatation of the transverse and ascending aorta with opacity of the aortic window. The pulmonary artery was enlarged and its pulsations increased. There was moderate enlargement of the left ventricle, and it appeared also that the right atrium was somewhat dilated. (Fig. 1.)

The electrocardiogram (Fig. 2) showed prominent S waves in leads I and V_6 and a high R in V_1. P waves were notched and T waves inverted in $V_{1, 2, 3, 4}$, diphasic in V_5. The electrocardiogram was believed to indicate right ventricular hypertrophy.

The tentative diagnosis on the basis of the initial study was syphilitic aneurysm of the ascending aorta with erosion into the pulmonary artery.

The symptoms of congestive failure responded readily to rest, digitalization, mercurial diuretics and a low salt diet. After subsidence of the heart failure an intravenous angiocardiogram was performed but satisfactory visualization of the aorta was not obtained. Cardiac catheterization (Fig. 3) revealed right ventricular pressure of 63/5 mm. Hg with the O_2 content essentially the same as that in the superior vena cava. As the catheter passed into the main pulmonary artery the oxygen content rose 6 vol. per cent. The pressure in this vessel was 63/8. Mean pulmonary capillary pressure was 26. Arterial oxygen saturation was 95 per cent and reached 100 per cent with inhalation of 100 per cent oxygen. Left ventricular output was calculated at 3.4 L. per minute and it was estimated that the pulmonary flow was about three times the systemic flow.

Following the study the patient was discharged and followed in the Outpatient Clinic. After nineteen months he remained in a fair state of health.

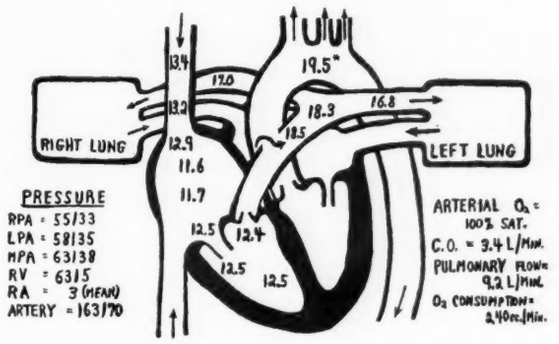

FIG. 3. Cardiac catherization results. Note the high right ventricular pressure and the 6 volume per cent elevation in O_2 content of the pulmonary artery as compared to that of the right ventricle. Asterisk denotes sample from left brachial artery.

COMMENTS

Although the subjective symptoms of this patient merely indicated congestive heart failure of fairly rapid onset, the physical signs were strongly suggestive of a communication between the aorta and the pulmonary artery, either a patent ductus or rupture of an aneurysm into the pulmonary artery. The findings on cardiac catheterization proved the presence of such a communication, and indicated that the fistula was of moderate size. The positive serologic tests for syphilis, the x-ray evidence of dilatation of the aorta and the rather sudden onset of symptoms made it fairly certain that the communication between the aorta and pulmonary artery was not a patent ductus but rather a fistulous connection with an aneurysm of the aorta.

SUMMARY

A case is reported in which erosion of an aneurysm of the aorta into the pulmonary artery, with production of a fistula between these two vessels, was proved by cardiac catheterization.

The patient was alive and in a fair state of health nineteen months after the episode occurred.

The diagnosis and pathophysiology of this condition is discussed.

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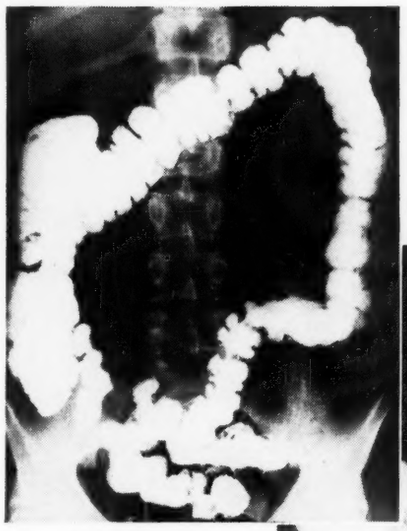

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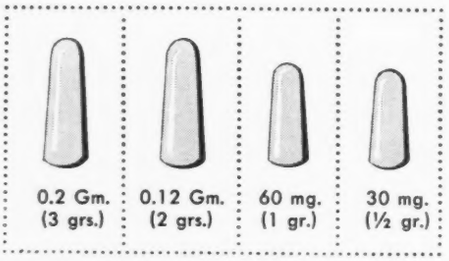

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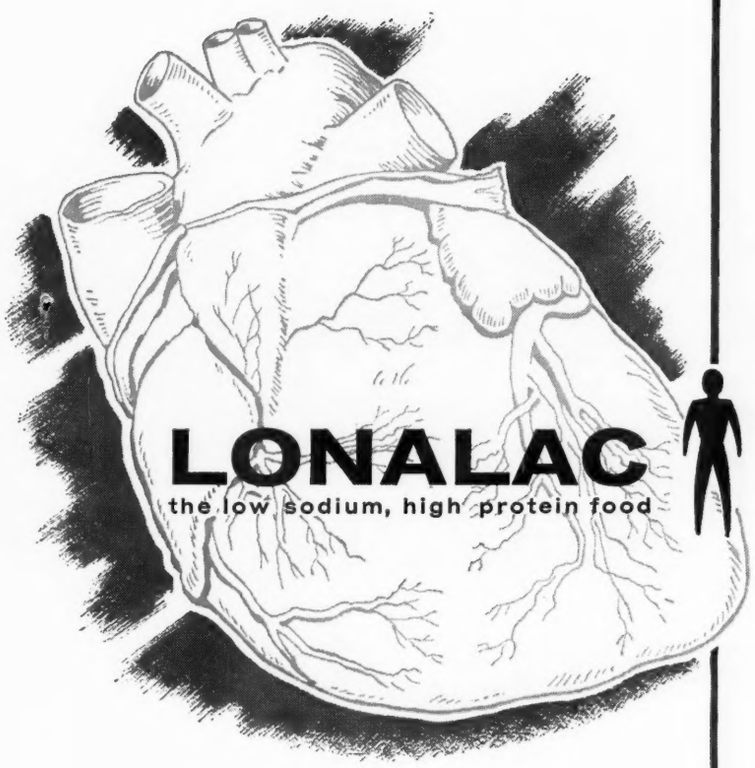

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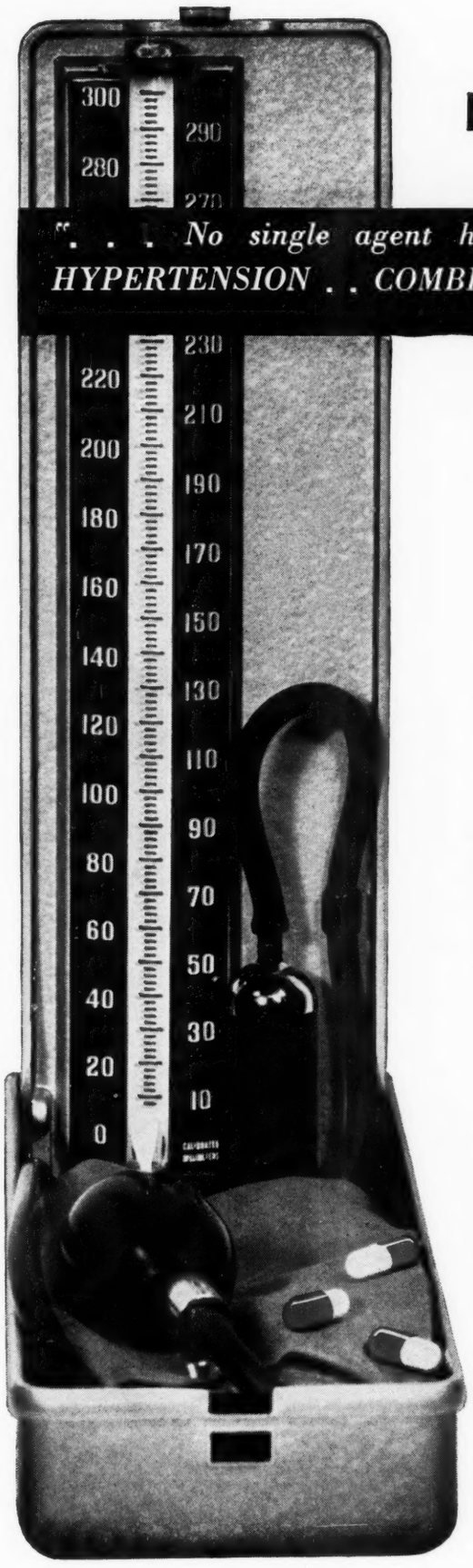

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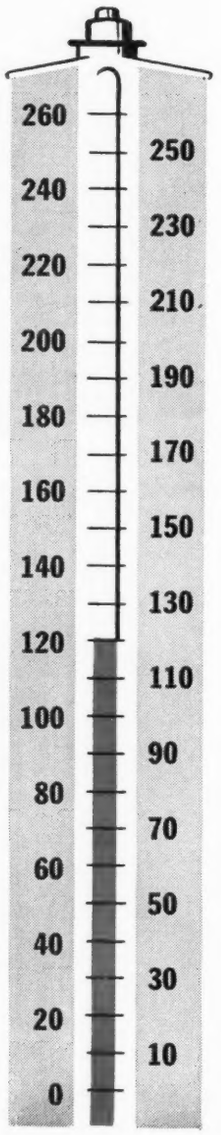

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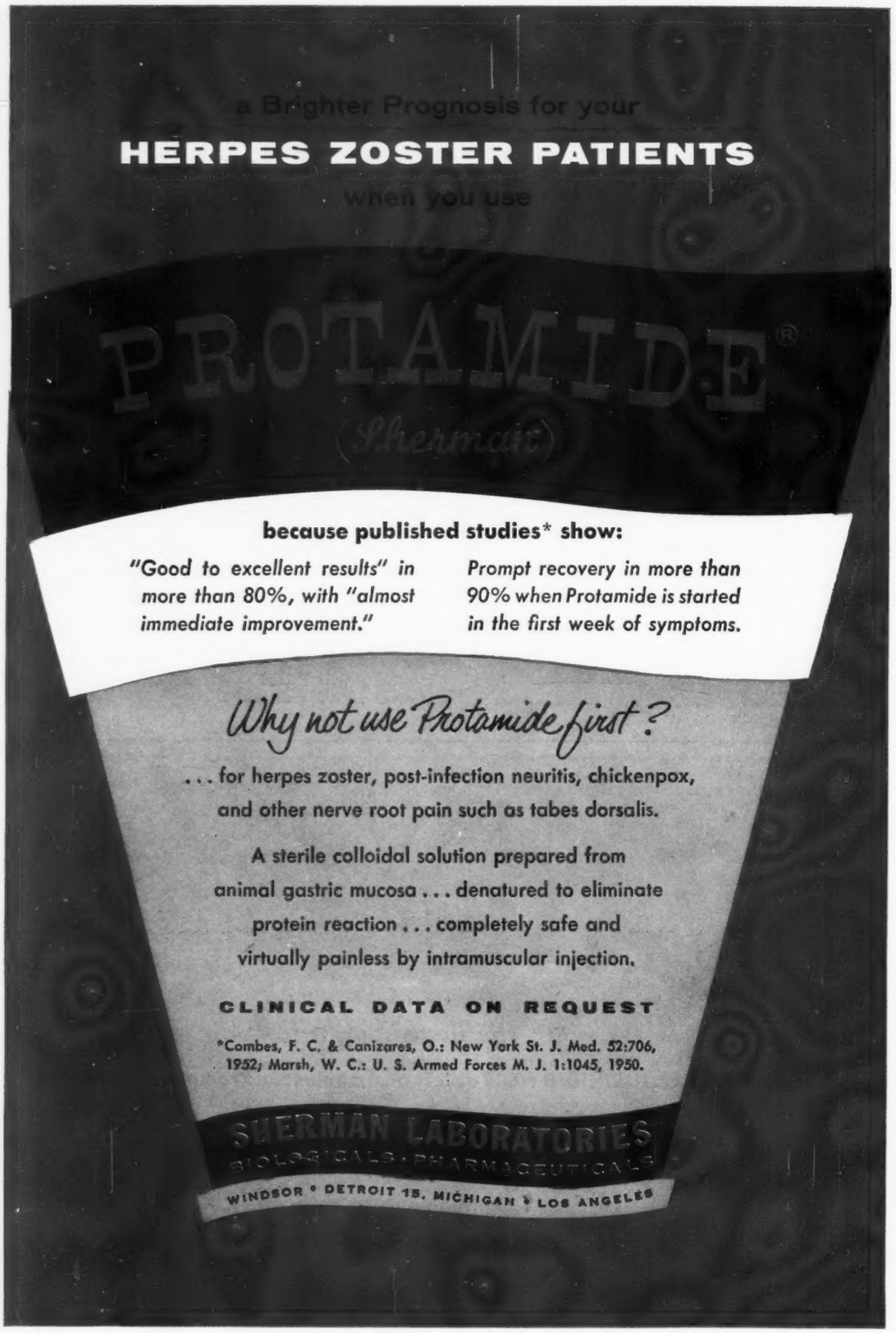
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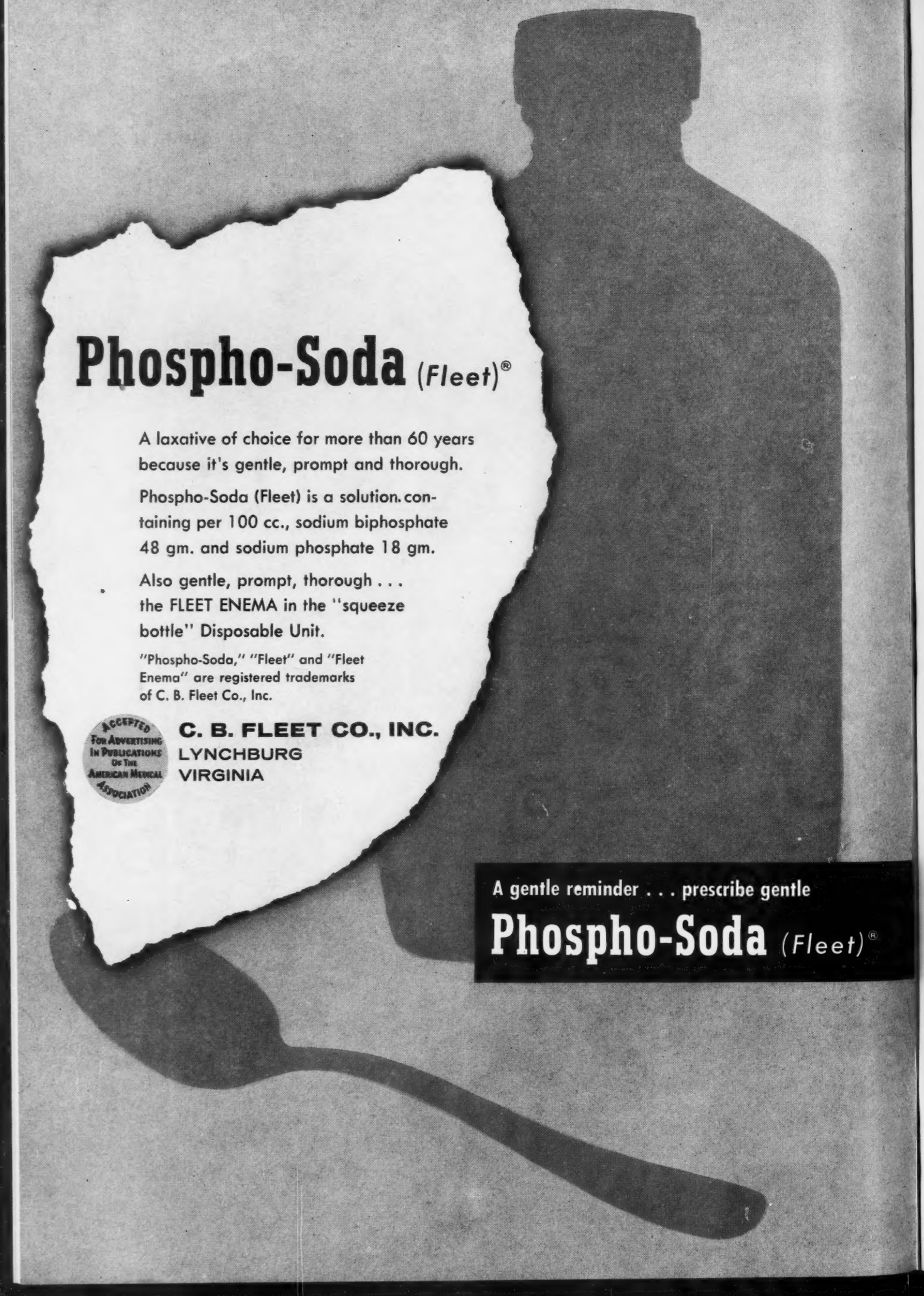
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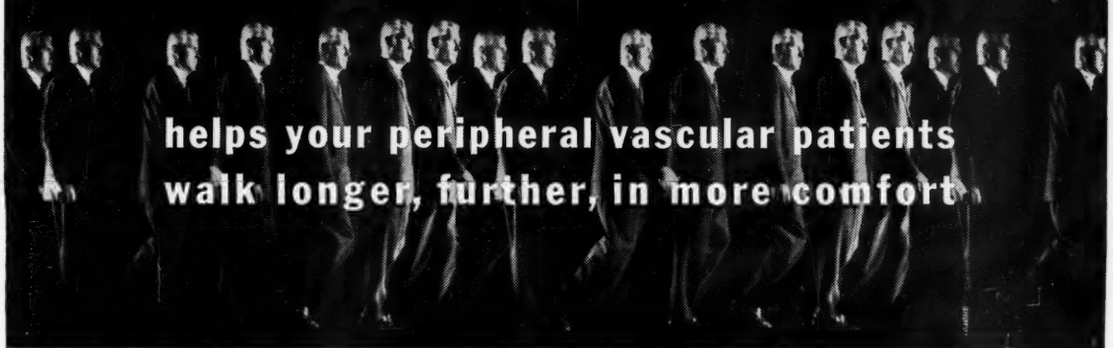

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2. Freedman, L.: Angiology 6:52, Feb. 1955.

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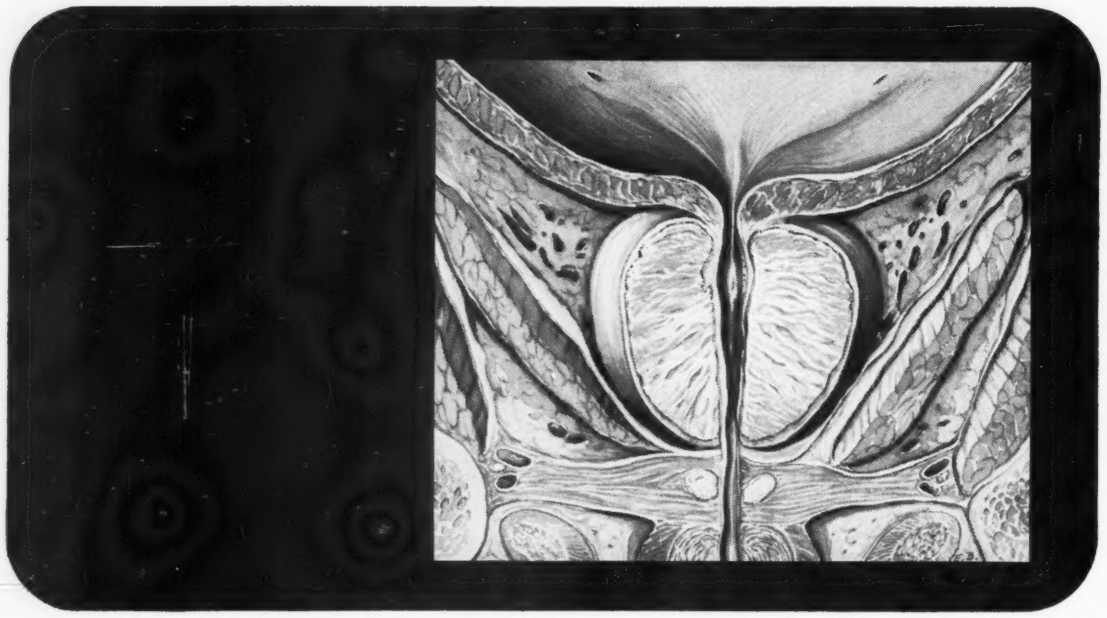

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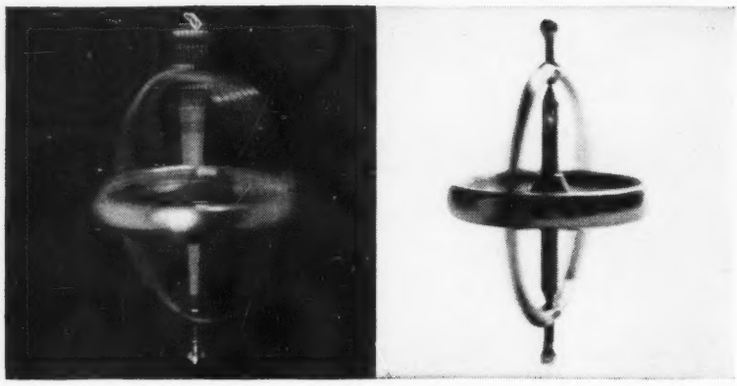

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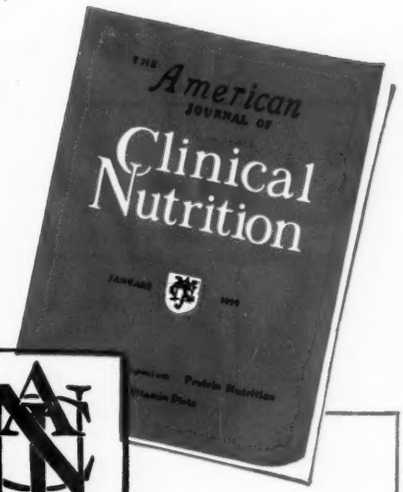

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1. Wood, H. F., and McCarty, M.: Am. J. Med. *17*:768 (Dec.) 1954. 2. Stollerman, G. H., et al.: Am. J. Med. *15*:645 (Nov.) 1953. 3. Rantz, L. A.: Disease-a-Month *1*:18 (Oct.) 1954. 4. Kroop, I. G., and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. *86*:95 (May) 1954. 5. McEwen, C.: M. Clin. North America (Mar.) 1955, to be published.

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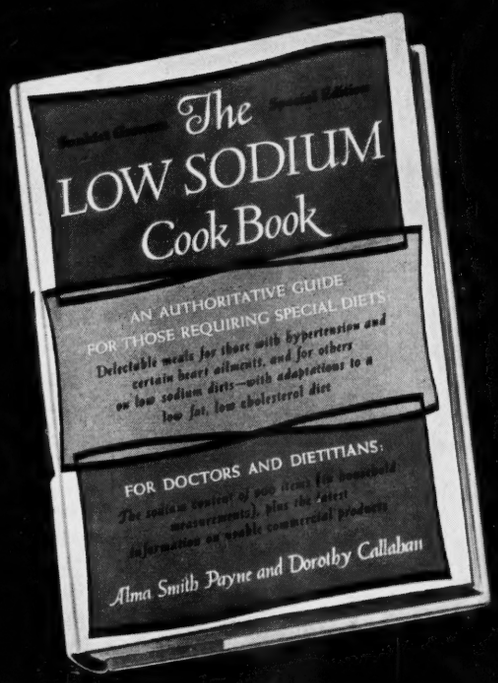

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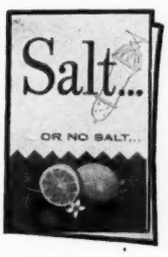

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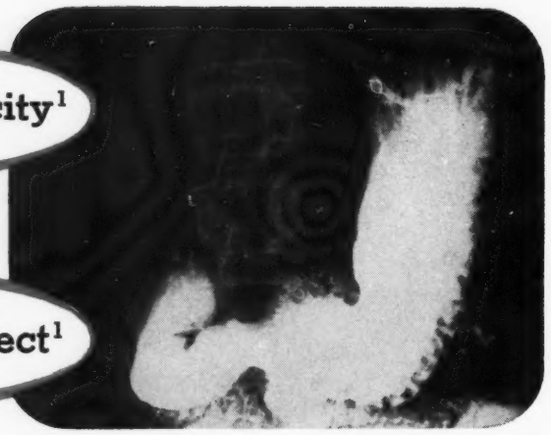

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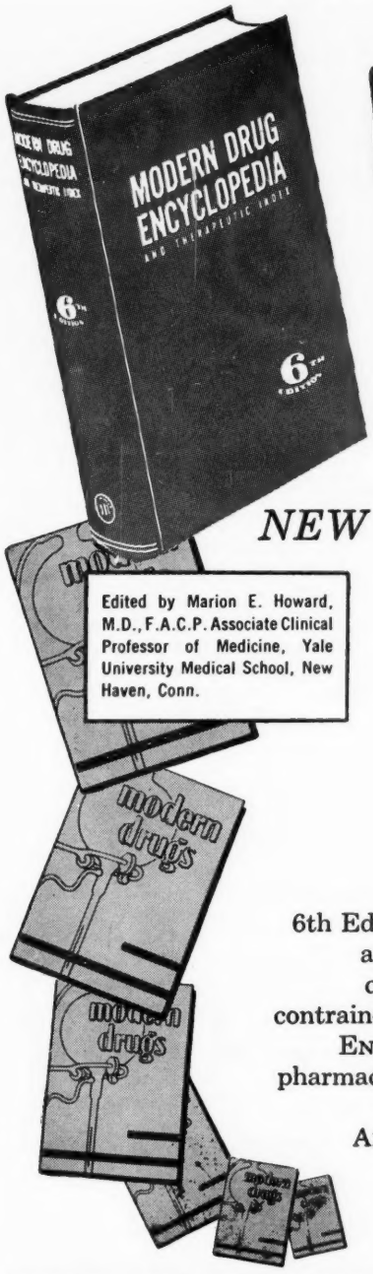
2. Morrison, Samuel: Magnesium Aluminum Hydroxide Gel in the Antacid Therapy of Peptic Ulcer, Am. J. Gastroenterology 22:309 (1954).



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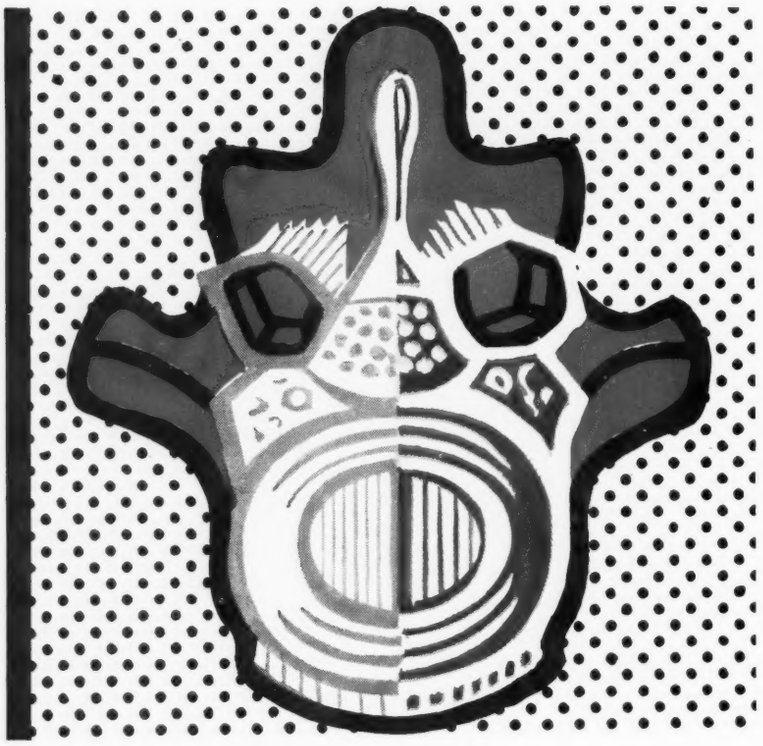

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(1) Payne, R. W.; Shetlar, M. R.; Farr, C. H.; Hellbaum, A. A., and Ishmael, W. K.: J. Lab. & Clin. Med. *45*:331, 1955. (2) Bunim, J. J.; Williams, R. R., and Black, R. L.: J. Chron. Dis. *1*:168, 1955. (3) Holbrook, W. P.: M. Clin. North America *39*:405, 1955.

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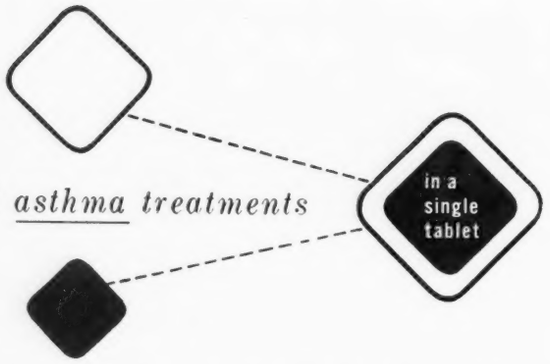

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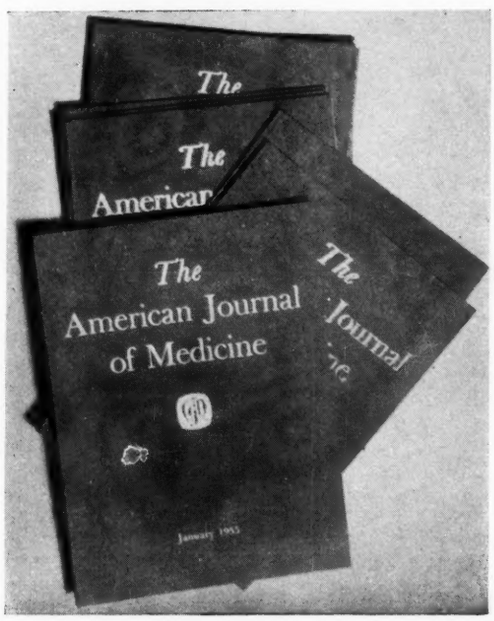

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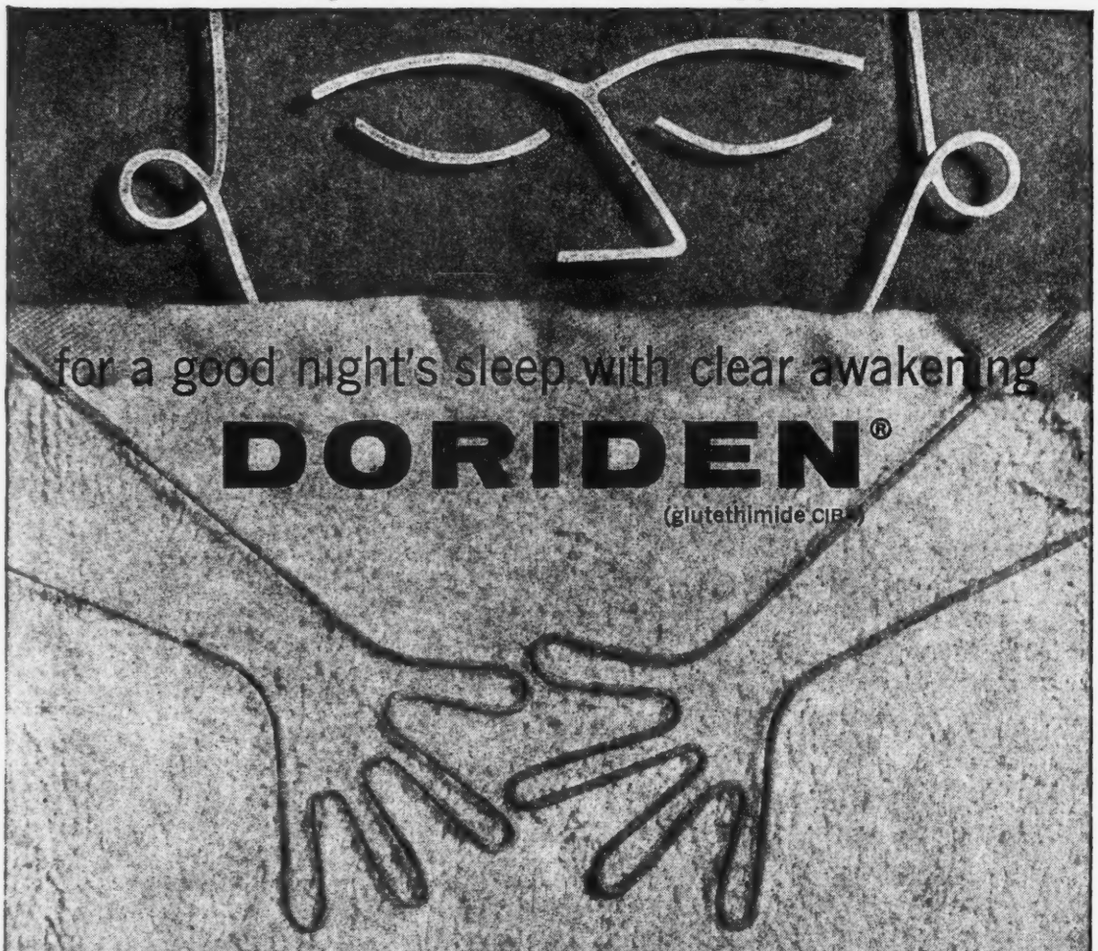

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